Geoeconomic variations in epidemiology, ventilation management, and outcomes in invasively ventilated intensive care unit patients without acute respiratory distress syndrome: a pooled analysis of four observational studies

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Summary

Background Geoeconomic variations in epidemiology, the practice of ventilation, and outcome in invasively ventilated intensive care unit (ICU) patients without acute respiratory distress syndrome (ARDS) remain unexplored. In this analysis we aim to address these gaps using individual patient data of four large observational studies.

Methods In this pooled analysis we harmonised individual patient data from the ERICC, LUNG SAFE, PRoVENT, and PRoVENT-iMiC prospective observational studies, which were conducted from June, 2011, to December, 2018, in 534 ICUs in 54 countries. We used the 2016 World Bank classification to define two geoeconomic regions: middle-income countries (MICs) and high-income countries (HICs). ARDS was defined according to the Berlin criteria. Descriptive statistics were used to compare patients in MICs versus HICs. The primary outcome was the use of low tidal volume ventilation (LTVV) for the first 3 days of mechanical ventilation. Secondary outcomes were key ventilation parameters (tidal volume size, positive end-expiratory pressure, fraction of inspired oxygen, peak pressure, plateau pressure, driving pressure, and respiratory rate), patient characteristics, the risk for and actual development of acute respiratory distress syndrome after the first day of ventilation, duration of ventilation, ICU length of stay, and ICU mortality.

Findings Of the 7608 patients included in the original studies, this analysis included 3852 patients without ARDS, of whom 2345 were from MICs and 1507 were from HICs. Patients in MICs were younger, shorter and with a slightly lower body-mass index, more often had diabetes and active cancer, but less often chronic obstructive pulmonary disease and heart failure than patients from HICs. Sequential organ failure assessment scores were similar in MICs and HICs. Use of LTVV in MICs and HICs was comparable (42·4% *vs* 44·2%; absolute difference –1·69 [–9·58 to 6·11] p=0·67; data available in 3174 [82%] of 3852 patients). The median applied positive end expiratory pressure was lower in MICs than in HICs (5 [IQR 5–8] *vs* 6 [5–8] cm H_2O; p=0·0011). ICU mortality was higher in MICs than in HICs (30·5% *vs* 19·9%; p=0·0004; adjusted effect 16·41% [95% CI 9·52–23·52]; p<0·0001) and was inversely associated with gross domestic product (adjusted odds ratio for a US$10 000 increase per capita 0·80 [95% CI 0·75–0·86]; p<0·0001).

Interpretation Despite similar disease severity and ventilation management, ICU mortality in patients without ARDS is higher in MICs than in HICs, with a strong association with country-level economic status.

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Introduction

Variations in human and structural resources in middle-income countries (MICs) might affect management of critically ill patients.[1–3] Typical differences between MICs and high-income countries (HICs) have been described for diagnostic approaches in respiratory failure,[4] haemodynamic management,[5–7] and care of the ventilated patient.[1,8,9] Epidemiology in critically ill patients might depend on geoeconomic status.[9,10] Non-modifiable factors such as a tropical setting and organisational factors, but also differences in disease severity and presence of comorbidities, might lead to substantial dissimilarities between MICs and HICs. Inequalities in distribution of income might further affect patients' outcomes, as has been shown before in patients with heart failure.[11,12]

The large observational study to understand the global impact of severe acute respiratory failure (LUNG SAFE)[13]

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed with the terms "mechanical ventilation, adult" [MeSH terms] AND "adult" [all fields] AND "respiratory" [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 Feb 28, 2021. We also reviewed the reference lists of publications identified by this search. We found several national and multinational studies of epidemiology, management, and outcomes related to ventilation. We also identified one secondary analysis focusing on geoeconomic variations in acute respiratory distress syndrome (ARDS). Yet, no study analysed variations across major geoeconomic groupings for ventilated patients without ARDS. The number of patients receiving invasive ventilation, however, is steadily growing in middle-income countries (MIC). It remains unclear whether shortages in resources might compromise care for critically ill patients, including ventilation in patients without ARDS.

Added value of this study

Our analysis of four large observational studies provides detailed information on epidemiology, important aspects of ventilation management, and outcomes in a large cohort of ventilated patients without ARDS from 54 countries. We report ventilation data over 4 consecutive days, allowing for detailed temporal insight into ventilation management. We identified notable differences in epidemiology between patients from MICs versus patients from high-income countries (HICs). Baseline severity scores and ventilation management were remarkably similar, in particular, the use of lung-protective ventilation was equally applied across both groups. Nevertheless, geoeconomic status had a strong association with mortality.

Implications of all the available evidence

Important regional differences exist in the demographics, but diseases severity and ventilation management are not different between MICs and HICs. Restrictions in resources do not seem to affect the ability to apply lung-protective ventilation in patients without ARDS, but heavily influence patients' outcome.

investigators showed notable differences in demographics, disease severity, ventilation management, and mortality in ventilated patients with acute respiratory distress syndrome (ARDS) across geoeconomic regions, and that survival is associated with gross national income.[9] Even when limiting the analysis to patients with mild ARDS, one in every three patients had a poor outcome.[14] One key aspect of ventilator management in ARDS is the use of lung-protective ventilation, in particular low tidal volume ventilation (LTVV).[15] LUNG SAFE showed that significantly more patients with ARDS received LTVV in HICs than in MICs.[9]

Most intensive care unit (ICU) patients receive invasive ventilation for a reason other than ARDS,[16–18] even if the epidemiology of ventilated patients is being heavily changed by the current COVID-19 pandemic.[19] It is uncertain whether similar differences in epidemiology, ventilation management, and outcomes exist in these patients across geoeconomic regions. The aim of the current pooled analysis using individual patient data of four large observational studies therefore was to investigate and compare the epidemiology, ventilation management, and outcomes in patients without ARDS in MICs and HICs. The main hypothesis was that use of LTVV differs between MICs and HICs.

Methods

Study design and participants

In this pooled analysis, individual data of patients without ARDS were extracted from the databases of four large prospective observational investigations into ventilation management in critically ill patients between June, 2011, and December, 2018: the epidemiology of respiratory insufficiency in critical care (ERICC) study (773 patients without ARDS in Brazil),[20] LUNG SAFE (1069 patients without ARDS in 50 countries),[13] the practice of ventilation in critically ill patients without ARDS (PRoVENT) study (1021 patients without ARDS in 16 countries),[16] and the practice of ventilation in critically ill patients in MICs (PROVENT-iMiC) study (1315 patients without ARDS in ten countries in southeast Asia).[21] LUNG SAFE, PRoVENT, and the PRoVENT-iMiC studies enrolled patients during a 4-week period; ERICC enrolled patients during a 2-month period. Patients diagnosed with ARDS on admission to hospital, those who received only non-invasive ventilation, and those with incomplete data were excluded. Our analysis has no separate ethics approval because it is pooling data from four approved studies, with the individual steering committees approving the use of the data. The need for patients' informed consent was waived in most centres in all four observational studies, as detailed in the original manuscripts of these studies. Detailed study methods of the four studies have been reported elsewhere.[13,16,20–22]

Outcomes

The primary outcome was use of LTVV, defined as receiving ventilation with a tidal volume equal to or less than 8 mL/kg predicted bodyweight, for the first 3 days of mechanical ventilation. Secondary outcomes were tidal volume size (expressed in modus [most used value] absolute tidal volume, in mL/kg actual body weight, and in mL/kg predicted body weight), positive end-expiratory pressure, fraction of inspired oxygen, peak pressure, plateau pressure, driving pressure, and respiratory rate. Other secondary outcomes included epidemiological and clinical endpoints, such as patient characteristics, the

risk for and actual development of ARDS after the first day of ventilation, duration of ventilation, ICU length of stay, and ICU mortality.

Definitions and calculations

All datasets and definitions were harmonised before pooling the data, according to the case report forms and data dictionaries of the four studies. Participation of investigators from all four original studies was sought in the process. ARDS was defined according to the Berlin definition for ARDS.[23] Risk of ARDS was defined by a lung injury prediction score of 4 or more.[24] Disease severity at baseline was assessed using the sequential organ failure assessment (SOFA) score.[25]

Driving pressure was calculated by subtracting the level of positive end-expiratory pressure from the plateau pressure in volume-controlled ventilation, or from maximum inspiratory pressure in pressure-controlled ventilation, and only in patients with evidence of absence of spontaneous ventilation (defined as patients having equal set and measured respiratory rate, and not receiving ventilatory support via a spontaneous breathing mode).

Income of individual countries was assessed by the gross domestic product (GDP) per capita, a measure of a country's economic output that divides the country's national income by its total population.[26]

The 2016 World Bank countries classification was used to define two groupings: patients in ICUs in MICs and patients in ICUs in HICs.[26]

Statistical analysis

Descriptive statistics were used to compare patients in MICs versus HICs, using frequencies and proportions for categorical variables, and medians with IQRs for continuous variables. For baseline characteristics, the groups were compared using Fisher's exact tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. In all analyses, HICs were used as a reference.

All analyses were performed using multilevel (patients nested in hospitals nested in countries), mixed modelling with hospitals and countries as random effects. Ventilatory variables and parameters were compared among the groups, and absolute differences with the respective 95% CI were calculated as the absolute difference from a mixed-effect linear model considering the hospitals and countries as random effects to account for within-centre clustering. Categorical variables were compared as the risk difference from the same model.

Outcomes were compared between the two groups with the unadjusted risk difference extracted from the model described earlier. Additionally, all clinical outcomes were further compared after adjustment for prognostic factors in parsimonious models, considering the following variables, selected according to clinical relevance: age, type of admission (medical, surgical

	Middle-income countries (n=2345)	High-income countries (n=1507)	p value
Age, years	60 (43–72)	64 (52–75)	<0·0001
Gender			
Female	941/2325 (40·5%)	530/1501 (35·3%)	
Male	1384/2325 (59·5%)	971/1501 (64·7%)	0·0015
Height, cm	165 (160–170)	170 (163–177)	<0·0001
Weight, kg	70 (62–80)	76 (65–89)	<0·0001
Body-mass index, kg/m²	25 (22–28)	26 (23–29)	<0·0001
Type of admission	..	..	<0·0001
Medical	1443/2321 (62·2%)	848/1496 (56·7%)	..
Surgical elective	401/2321 (17·3%)	289/1496 (19·3%)	..
Surgical urgency	322/2321 (13·9%)	282/1496 (18·9%)	..
Trauma	155/2321 (6·7%)	77/1496 (5·1%)	..
Lung injury prediction score*	4 (3–6)	4 (2–6)	<0·0001
Number at risk of ARDS	953/1508 (63·2%)	257/653 (39·4%)	<0·0001
Sequential organ failure assessment score			
Total	7 (5–10)	7 (5–10)	0·033
Neurological	3 (0–4)	2 (0–4)	0·070
Renal	0 (0–2)	1 (0–3)	<0·0001
Respiratory	2 (0–3)	2 (2–3)	<0·0001
Haematological	1 (1–1)	0 (0–1)	<0·0001
Liver	0 (0–0)	0 (0–1)	0·0047
Circulatory	0 (0–3)	1 (0–2)	0·96
Comorbidities			
Chronic obstructive pulmonary disease	207/2323 (8·9%)	294/1482 (19·8%)	<0·0001
Diabetes	600/2324 (25·8%)	316/1489 (21·2%)	0·0014
Chronic kidney disease	262/2324 (11·3%)	163/1490 (10·9%)	0·79
Active cancer	322/2321 (13·9%)	169/1484 (11·4%)	0·029
Immunosuppression	73/1095 (6·7%)	103/1490 (6·9%)	0·87
Haematological cancer	52/2063 (2·5%)	21/854 (2·5%)	1·00
Heart failure	227/2324 (9·8%)	190/1487 (12·8%)	0·0044
Chronic liver failure	99/2324 (4·3%)	52/1489 (3·5%)	0·27
Risk factors for ARDS			
Pneumonia	528/2324 (22·7%)	416/1491 (27·9%)	0·0003
Non-pulmonary sepsis	329/1702 (19·3%)	167/1491 (11·2%)	<0·0001
Gastric aspiration	151/2324 (6·5%)	172/1491 (11·5%)	<0·0001
Pancreatitis	2/215 (0·9%)	17/854 (2·0%)	0·45
Trauma	163/2344 (7·0%)	83/1507 (5·5%)	0·085
Smoke inhalation	34/1723 (2·0%)	23/1507 (1·5%)	0·41
Pulmonary contusion	29/1702 (1·7%)	52/1491 (3·5%)	0·0020
Burn	2/215 (0·9%)	4/854 (0·5%)	0·77
Pulmonary vasculitis	1/215 (0·5%)	7/854 (0·8%)	0·92
Non-cardiogenic shock	319/2345 (13·6%)	129/1507 (8·6%)	<0·0001
Near-drowning	3/1723 (0·2%)	1/1507 (0·1%)	0·71
Drug overdose	4/215 (1·9%)	23/854 (2·7%)	0·65
Transfusion-related acute lung injury	8/215 (3·7%)	26/854 (3·0%)	0·77
Limitation of support	65/1701 (3·8%)	203/1486 (13·7%)	<0·0001

Data are median (IQR) or n/N (%). ARDS=acute respiratory distress syndrome. *Data available in 2161 (56·1%) of 3852 patients.

Table 1: **Baseline characteristics of patients**

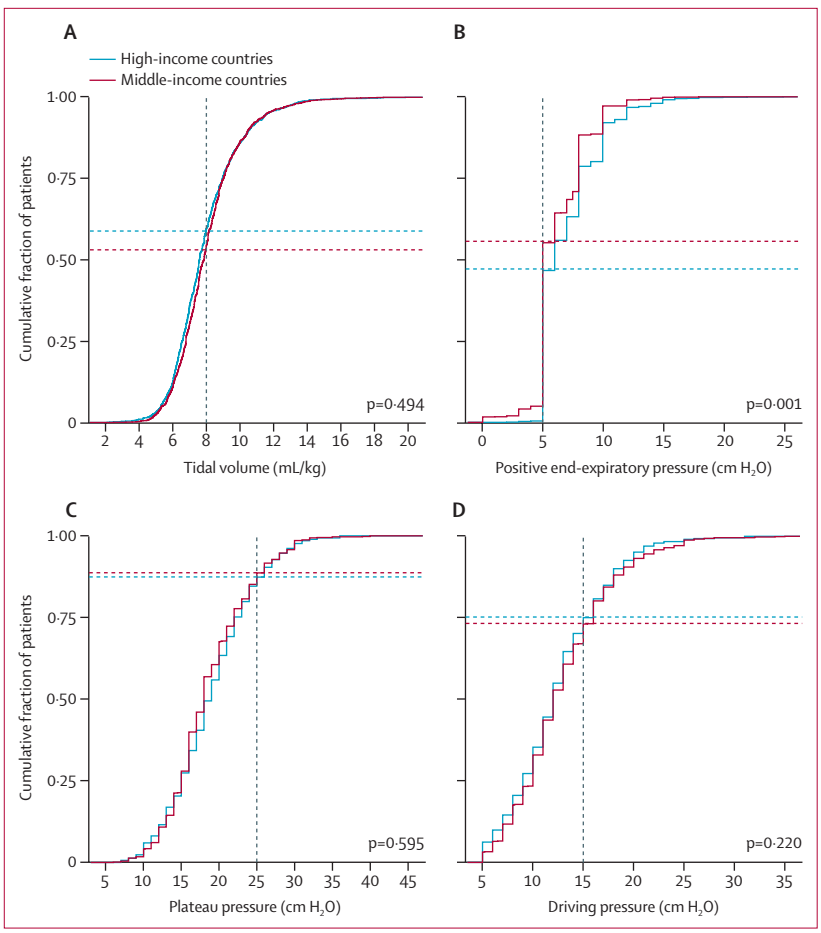

Figure 1: **Ventilation parameters on the first day of mechanical ventilation in patients stratified by economic group**

Cumulative frequency distribution of tidal volume (A), positive end-expiratory pressure (B), plateau pressure (C), and driving pressure (D). Vertical dotted lines represent the cutoff for each variable and horizontal dotted lines represent the respective proportion of patients reaching each cutoff.

elective, surgical urgency, and trauma), active cancer, the partial pressure of arterial oxygen to the fraction of inspired oxygen ratio on the day ventilation started, total SOFA score on the day ventilation started, and an interaction between SOFA score and income group.

Cumulative distribution plots were used to plot the cumulative distribution frequency of ventilation variables on the day ventilation started, using vertical dotted lines to show cutoffs for each variable and horizontal dotted lines to indicate proportions of patients reaching the cutoffs. Cutoffs to form matrices were based on widely accepted values for each variable (8 mL/kg predicted bodyweight for tidal volume, 5 cm H_2O for positive end-expiratory pressure, 30 cm H_2O for plateau pressure, and 15 cm H_2O for driving pressure).

Duration of ventilation was assessed in a competing risk model with death before extubation treated as competing risk. The results were described with the use of cumulative incidence function and reported as subdistribution hazard ratio with 95% CI estimated from a Fine-Gray model considering the cluster of the data. Duration of ventilation and ICU length of stay were censored at day 28 for this analysis.

In addition to the adjusted odds ratio for ICU mortality described in the models above, the results were also presented as the predicted mortality rate according to the baseline risk model including SOFA score at day 1 in each group (marginal effect plots).

A scatterplot was used to explore the associations between crude ICU mortality and individual country's GDP per capita. A variable life-adjusted display (VLAD) was plotted to assess the cumulative difference in survival according to income groups. VLAD is presented as the cumulative excess of survival by age, and was computed according to the difference of the expected and observed ICU mortality, with the expected mortality being derived from the baseline risk model. When a patient survived, their probability of death was added and when a patient died, their probability of death was removed. The VLAD analysis was corrected by the total number of patients in each group. The performance of the baseline risk model was assessed according to its discrimination (area under the curve) and calibration (through calibration belts). Finally, attributable fraction analysis was used to assess the proportion of ICU deaths attributable to admissions in MICs, considering the cluster of the data. Only complete case analyses were carried out.

The rate of missing data is shown in the appendix (pp 7–8) and a sensitivity analysis for the clinical outcomes considering multiple imputation for missing data was performed. Multiple imputation used chained equations considering baseline variables and outcomes, and five imputed datasets. All analyses were conducted in R (v.3.60) and a p value below 0·05 was considered statistically significant.

Role of the funding source

There was no funding source for this study.

Results

Of the 7608 patients included in the ERICC, LUNG SAFE, PRoVENT, and PRoVENT-iMiC studies, 3852 patients without ARDS from 534 ICUs across six continents were included in our analysis (appendix p 2). Of these patients, 2345 (61·5%) were in 27 MICs and 1507 (38·5%) were in 27 HICs. Characteristics of participating centres, economic status of the groups, and number of patients recruited per country are reported in the appendix (pp 9–10). There was a four-fold difference in median GDP per capita between MICs and HICs, with a large range of GDP among studied countries (from $US777 to $81000). Non-academic hospitals were more common in MICs. The number of physicians per ICU was higher in HICs, but the number of nurses per bed was similar in MICs and HICs.

Patients in MICs had significantly lower age, height, and body-mass index (BMI; table 1). SOFA scores at ICU admission were not different between MICs and HICs.

Patients in MICs had diabetes and active cancer more often, were more frequently classified as non-surgical patients, and more often had sepsis and non-cardiogenic shock as the reason for ICU admission. Chronic obstructive pulmonary disease and heart failure were more common in patients from HICs. Limitation of support was more frequently reported in HICs. Ventilator settings and parameters are shown in figure 1, table 2, and the appendix (p 3). Use of LTVV in the first 3 days was comparable between patients in MICs and patients in HICs (42·4% *vs* 44·2%; absolute difference –1·69% [95% CI –9·58 to 6·11]; p=0·67; table 2). Tidal volume expressed in mL/kg actual bodyweight and predicted bodyweight was not different between patients in MICs and HICs, with a lower applied absolute median tidal volume used in MICs. A comparable distribution of tidal volume was observed between the two groups (appendix p 4). The difference in applied positive end-expiratory pressure, peak and plateau pressure, driving pressure, fraction of inspired oxygen, and respiratory rate was not meaningfully different between HICs and MICs. Arterial CO_2 pressure was lower in patients in MICs.

Patients in MICs had a higher risk of ARDS than patients in HICs according to the lung injury prediction score (63·2% *vs* 39·4%; p=0·020; table 3). However, development of ARDS after start of ventilation, duration of ventilation, and ICU length of stay were similar in patients in MICs and in HICs. When accounting for the competing risk of death before extubation, the probability over time of extubation was similar in patients from MICs versus HICs (appendix p 5).

ICU mortality was approximately 1·5-fold higher in patients from MICs than from HICs. The higher probability of death in patients in MICs was particularly pronounced in patients with lower SOFA scores (figure 2A). In patients older than 50 years, cumulative excess survival was lower in MICs, and the gap

	Middle-income countries (n=2345)	High-income countries (n=1507)	Absolute difference (95% CI)*	p value
Primary outcome				
Use of LTVV in first 3 days†	752/1775 (42·4%)	619/1399 (44·2%)	–1·69 (–9·58 to 6·11)	0·67
Day 1				
Use of LTVV†	933/1762 (53·0%)	810/1379 (58·7%)	–5·62 (–12·54 to 1·27)	0·12
Tidal volume, mL	458 (400 to 500)	495 (430 to 552)	–33·19 (–51·01 to –15·44)	0·0010
Mode	500	500	..	..
Tidal volume, mL/kg predicted bodyweight	7·9 (6·8 to 9·1)	7·6 (6·6 to 9·0)	0·10 (–0·19 to 0·39)	0·49
Tidal volume, mL/kg actual bodyweight	6·8 (5·8 to 7·7)	6·4 (5·4 to 7·8)	0·09 (–0·30 to 0·48)	0·65
PEEP, cm H_2O	5 (5 to 8)	6 (5 to 8)	–1·04 (–1·62 to –0·46)	0·0011
FiO_2	0·50 (0·40 to 0·60)	0·50 (0·40 to 0·60)	0·00 (–0·04 to 0·04)	0·88
Peak pressure, cm H_2O	22 (18 to 27)	22 (18 to 27)	0·91 (–1·00 to 2·84)	0·36
Plateau pressure, cm H_2O	18 (15 to 22)	19 (15 to 22)	–0·44 (–2·01 to 1·16)	0·59
Driving pressure, cm H_2O	12 (10 to 16)	12 (9 to 15)	0·95 (–0·50 to 2·43)	0·22
Total respiratory rate, mpm	17 (14 to 20)	16 (14 to 20)	0·60 (–0·71 to 1·92)	0·36
Arterial pH	7·36 (7·29 to 7·42)	7·36 (7·29 to 7·43)	–0·01 (–0·02 to 0·01)	0·59
PaO_2/FiO_2	240 (162 to 347)	210 (150 to 278)	15·48 (–12·71 to 43·15)	0·28
$PaCO_2$, mm Hg	37·0 (31·1 to 44·0)	41·0 (36·0 to 48·8)	–4·90 (–6·54 to –3·23)	<0·0001
Day 2				
Use of LTVV†	788/1391 (56·6)	611/1064 (57·4)	–0·70 (–7·24 to 5·67)	0·83
Tidal volume, mL	450 (400 to 500)	500 (427 to 572)	–38·66 (–57·93 to –18·92)	0·0006
Mode	500	500	..	..
Tidal volume, mL/kg predicted bodyweight	7·8 (6·8 to 8·9)	7·8 (6·7 to 9·0)	–0·04 (–0·35 to 0·27)	0·80
Tidal volume, mL/kg actual bodyweight	6·6 (5·7 to 7·6)	6·6 (5·5 to 7·8)	0·04 (–0·35 to 0·44)	0·83
PEEP, cm H_2O	5 (5 to 8)	6 (5 to 8)	–0·97 (–1·53 to –0·41)	0·0016
FiO_2	0·40 (0·35 to 0·50)	0·40 (0·35 to 0·50)	0·02 (–0·01 to 0·05)	0·31
Peak pressure, cm H_2O	21 (18 to 26)	21 (17 to 27)	0·66 (–1·33 to 2·64)	0·52
Plateau pressure, cm H_2O	18 (16 to 22)	19 (15 to 23)	–0·71 (–2·20 to 0·72)	0·35
Driving pressure, cm H_2O	13 (10 to 16)	12 (9 to 15)	0·49 (–0·87 to 1·88)	0·50
Total respiratory rate, mpm	18 (15 to 21)	18 (15 to 22)	0·24 (–1·06 to 1·54)	0·72
Arterial pH	7·39 (7·33 to 7·44)	7·39 (7·34 to 7·44)	0·00 (–0·01 to 0·02)	0·93
PaO_2/FiO_2	276 (196 to 370)	236 (178 to 312)	26·69 (3·89 to 49·27)	0·027
$PaCO_2$, mm Hg	36·0 (31·0 to 42·0)	40·0 (36·0 to 46·0)	–5·73 (–7·73 to –3·79)	<0·0001

(Table 2 continues on next page)

	Middle-income countries (n=2345)	High-income countries (n=1507)	Absolute difference (95% CI)*	p value
(Continued from previous page)				
Day 3				
Use of LTVV†	593/984 (60·3)	485/807 (60·1)	−0·90 (−8·09 to 6·05)	0·80
Tidal volume, mL	450 (400 to 500)	485 (427 to 568)	−36·71 (−57·23 to −15·31)	0·0017
Mode	500	450	..	..
Tidal volume, mL/kg predicted bodyweight	7·6 (6·7 to 8·8)	7·6 (6·5 to 9·0)	−0·07 (−0·40 to 0·26)	0·67
Tidal volume, mL/kg actual bodyweight	6·6 (5·7 to 7·6)	6·5 (5·5 to 7·7)	0·17 (−0·27 to 0·61)	0·47
PEEP, cm H_2O	6 (5 to 8)	6 (5 to 9)	−1·13 (−1·67 to −0·59)	0·0002
FiO_2	0·40 (0·30 to 0·50)	0·40 (0·30 to 0·50)	0·02 (−0·01 to 0·05)	0·22
Peak pressure, cm H_2O	22 (18 to 26)	21 (17 to 26)	1·34 (−0·58 to 3·27)	0·18
Plateau pressure, cm H_2O	18 (16 to 22)	19 (15 to 22)	0·03 (−1·50 to 1·6)	0·97
Driving pressure, cm H_2O	12 (10 to 16)	12 (9 to 15)	0·73 (−0·56 to 2·08)	0·30
Total respiratory rate, mpm	18 (15 to 22)	18 (15 to 23)	−0·52 (−1·76 to 0·72)	0·42
Arterial pH	7·40 (7·35 to 7·45)	7·41 (7·36 to 7·45)	0·00 (−0·02 to 0·01)	0·55
PaO_2/FiO_2	271 (195 to 360)	237 (175 to 306)	20·88 (−1·01 to 42·35)	0·066
$PaCO_2$, mm Hg	37·0 (32·0 to 43·0)	41·0 (37·0 to 46·7)	−4·78 (−6·58 to −2·97)	<0·0001

Data are median (IQR) or n/N (%). LTVV=low tidal volume ventilation. PEEP=positive end-expiratory pressure. FiO_2=fractional concentration of oxygen in inspired air. PaO_2=partial pressure of arterial oxygen. $PaCO_2$=partial pressure of arterial carbon dioxide. mpm=movements per min. *Absolute difference calculated from a mixed-effect linear model with study and groups as fixed effect and hospitals and country as random effect. †Denominators show the number of patients with available tidal volume and height data in which the use of LTVV could be assessed.

Table 2: **Ventilatory parameters in the first 3 days of mechanical ventilation**

	Middle-income countries (n=2345)	High-income countries (n=1507)	Unadjusted effect (95% CI)*	p value	Adjusted effect (95% CI)†	p value
Patients at risk of ARDS	953/1508 (63·2%)	257/653 (39·4%)	17·88 (4·32 to 31·49)‡	0·020	14·26 (3·30 to 25·25)‡	0·023
Development of ARDS during follow-up	184/2281 (8·1%)	151/1423 (10·6%)	−3·78 (−8·35 to 0·73)‡	0·11	−2·96 (−7·39 to 1·36)‡	0·19
Duration of ventilation, days	3·0 (1·0 to 7·0%)	4·0 (2·0 to 10·0%)	0·91 (0·80 to 1·05)§	0·20	0·93 (0·81 to 1·06)§	0·26
ICU length of stay, days	6·0 (2·0 to 12·0%)	7·0 (3·0 to 14·0%)	−1·00 (−4·31 to 2·26)¶	0·55	0·08 (−3·28 to 3·37)¶	0·96
ICU mortality	684/2243 (30·5%)	283/1419 (19·9%)	15·67 (7·98 to 23·60)‡	<0·0004	16·41 (9·52 to 23·52)‡	<0·0001

Data are median (IQR) or n/N (%). ARDS=acute respiratory distress syndrome. ICU=intensive care unit. *Unadjusted effect calculated from models with group as fixed effect and hospitals and countries as random effect. †Adjusted effect calculated from models with group as fixed effect, hospitals and countries as random effect, and adjusted for age, type of admission, active cancer, partial pressure of arterial oxygen to the fraction of inspired oxygen ratio at day 1, total sequential organ failure assessment (SOFA) score at day 1, and an interaction between SOFA and the group. ‡Effect estimate is risk difference from a mixed-effect model. §Effect estimate is subdistribution hazard ratio from a Fine-Gray model considering the cluster of the data. ¶Effect estimate is mean difference from a mixed-effect model.

Table 3: **Clinical outcomes according to the economic group**

increased with patient age (figure 2B; appendix p 5). The proportion of deaths attributable to admissions in MICs was 22·1% (95% CI 14·3–29·9; p<0·0001). Crude ICU mortality was inversely associated with GDP per capita (adjusted odds ratio for a US$10 000 increase in GDP per capita 0·80 [95% CI 0·75–0·86]; p<0·0001; figure 3). The sensitivity analysis after multiple imputation did not change the findings (appendix p 12). Characteristics and outcomes of patients with and without missing data in the primary outcome were comparable (appendix pp 13–14).

Discussion

The results of this pooled analysis of four large observational studies in invasively ventilated patients without ARDS can be summarised as follows: (1) the practice of ventilation, in particular the use of LTVV, does not differ between MICs and HICs; (2) in MICs more patients are at risk of ARDS but development of ARDS is comparable to that in HICs; (3) there are remarkable baseline differences between MICs and HICs regarding age, height, and comorbidities, but disease severity at ICU admission, ICU length of stay, and timing of extubation are similar in MICs and HICs; and (5) ICU mortality is significantly higher in MICs, with a strong association between country-level economic status and survival.

Strengths of this analysis are the availability of individual patient data of large groups of patients captured in more than 500 ICUs worldwide. All four studies had a

prospective design, and included measures to limit selection and observation bias. The short time span between the studies minimises the risk of effects of large changes in processes of care. The studies had several endpoints in common, which allowed for reliable merging of ventilation data. The statistical analysis plan for this meta-analysis was predefined and strictly followed.

MICs host a majority of the 14 million patients potentially in need of invasive ventilation each year.[18] The hypothesis that limitations in resources hamper physicians in MICs in applying LTVV[27–29] is rejected by the current analysis. This finding differs from the results of a 2017 study in patients with ARDS, whereby fewer patients in MICs received a tidal volume of less than 8 mL/kg predicted bodyweight than in non-European HICs, although the differences were small.[9] One salient finding of our study is that half of patients without ARDS did not receive LTVV. The benefit of LTVV has been clearly demonstrated for patients with ARDS, and there is potential benefit for patients without ARDS.[30,31] A 2018 randomised trial did not show a difference in ventilator-free days and alive at day 28 when comparing a low versus intermediate tidal volume strategy in patients without ARDS.[17] Yet because physician recognition of ARDS remains challenging,[13] and because patients who do not fulfil the current definition for ARDS still might have lung injury, targeting a low tidal volume in all patients has been suggested—ie, irrespective of the diagnosis of ARDS.[32]

A large difference in height was found among patients being ventilated in MICs versus HICs. This finding is important, as shorter patients and especially women with ARDS have been shown to be at higher risk of receiving higher tidal volume, although geoeconomic variations were not shown to modify the relationship between sex and mortality.[33,34] Beyond sex, variations in height depend on ethnicity-based anthropometric differences, nutritional status, and other population-specific characteristics. Our findings in patients without ARDS suggest that smaller absolute tidal volumes seem to be applied well in MICs, thus not affecting the use of lung-protective ventilation. Further research is needed to explore whether female patients without ARDS are at higher risk of injurious ventilation and poorer outcomes than men.

The difference in risk for ARDS in MICs and HICs seems not to be in line with the comparable proportion of patients actually developing ARDS in the two groupings. The lung injury prediction score performs poorly in predicting ARDS, as also suggested by one validation study[24] and subsequent investigations.[16,21,35] However, we cannot exclude the possibility that ARDS was underdiagnosed in ICUs in MICs. Although, physicians in MICs seem to recognise ARDS equally well or even better than those in HICs,[9,36] some ICUs might not have the resources to apply the Berlin definition for ARDS such as chest x-ray imaging and blood gas analysis.[4] In the PRoVENT-iMIC study performed in Asia, which reported

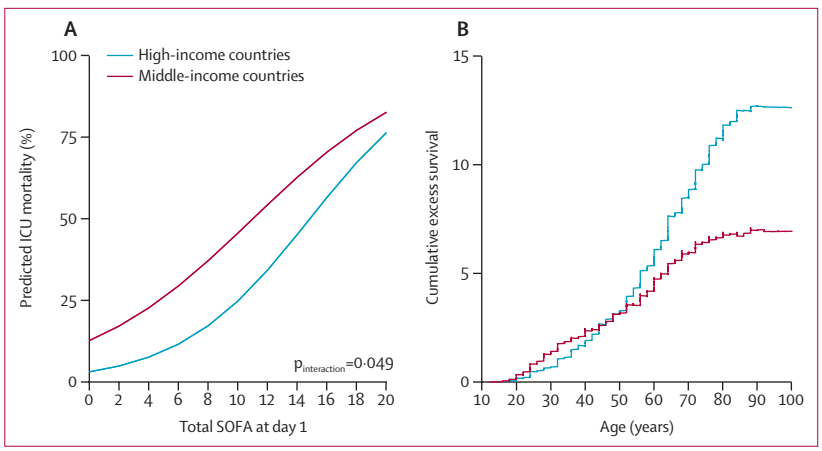

Figure 2: **Marginal effect plot (A) showing the predicted mortality according to the SOFA score at day 1 and variable life-adjusted display (B) to assess cumulative excess survival according to income groups**
ICU=intensive care unit. SOFA=sequential organ failure assessment.

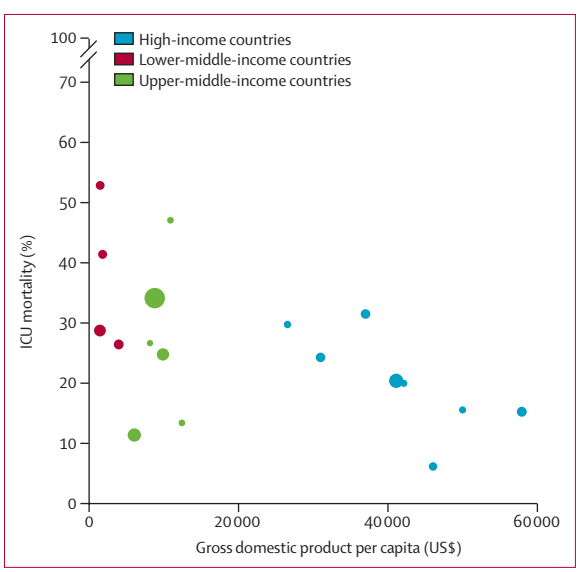

Figure 3: **Scatter plot exploring the association between crude intensive care unit mortality and gross domestic product per capita**
Each circle represents a country. The size of the circle reflects the number of enrolled patients in the country (appendix pp 8–9). Middle-income countries were further divided into lower-middle-income (red) and upper-middle-income countries (green). Countries that recruited fewer than 50 patients were excluded.

availability of diagnostic tools, x-ray apparatuses and blood gas analysers were available for over 90% of centres, although the resources were often shared with the hospital and not dedicated to the ICU.[21] LUNG SAFE was the only study to use an additional algorithm-based tool to identify patients who fulfilled the Berlin definition of ARDS.[13]

Although notable differences were found in demographics and comorbidities, there was neither a difference in diseases severity on ICU admission, nor in the practice of ventilation, between HICs and MICs. Thus, the higher ICU mortality in MICs requires alternative explanations. The SOFA score used to assess severity is predictive for mortality,[25] but this process

might need refinement in MICs. Beyond ventilator settings, there are additional ventilation management factors to consider.[1] For instance, differences in infection prevention and control policies might influence the rates of health-care-associated infections. Ventilator-associated pneumonia occurs more frequently and is more often caused by antimicrobial resistant pathogens in ICUs in Asia than in high-income settings.[37] Airway care also affects ventilation management, and acute endotracheal tube occlusions were reported in 38% of ventilated ICU patients in a 2015 Indian study.[38]

There is a wide range of potential factors at different levels of the care process that can contribute to the observed higher case fatality of mechanically ventilated patients in MICs. These factors include shortages in human and structural resources in low-income and MICs, limited use of treatment protocols, suboptimal ICU processes organisation, higher prevalence of antimicrobial drug resistance, higher bed-to-nurse ratio, or not having a daily plan of care review in place.[39,40] However, the quantitative contribution of these factors has not been well characterised.

Excess mortality in MICs increased with patient age, possibly reflecting a struggle in treating older patients who might have more comorbidities and reduced functional capacity. A 2018 study from Kenya showed high mortality despite the use of advanced therapies, with increased odds for mortality observed in age groups older than 35 years.[2] A lack of resources did not fully explain the differences in outcomes in ARDS patients,[9] and unmeasured social determinants might influence patients' prognosis.[41] Also, physicians in MICs might be more likely to accommodate families' requests to prematurely stop critical care on financial grounds, although our data did not corroborate this tendencey.[40,42] Differences in primary diagnosis and reason of admission to ICU might play a role—ie, more postoperative admissions in HICs than in MICs. Research agendas should explore these and other socioeconomic, demographic, genetic, and causative context-specific factors that interact to affect ICU mortality.

This analysis has limitations. The individual studies enrolled convenience samples, but with an over-representation of academic centres or teaching hospitals. This over-representation might affect the generalisability of the study findings to the wider MIC setting, because large public hospitals, known for their large patient load in relation to available medical staff and potential worse adherence to guidelines, were under-represented. The studies had no access to patients' source data; hence some degree of selection and reporting biases cannot be excluded. As with other analyses that pool data from large observational studies, residual confounding cannot be excluded. Missing tidal volumes or height data in some patients hampered assessing the use of LTVV. The number of patients recruited per country and ICU was highly heterogeneous. No data were available for pivotal characteristics such as functional status on admission; similarly, the SOFA score was the only severity score transversally available across the four studies, and thus described comorbidities are not included in the severity assessment. Also, only one low-income country was represented, which might reflect the resource-dense nature of ICU care.[9] Finally, economic status could only be analysed at a national level, and not at patient or family level.

In summary, there is no geoeconomic variation in the application of lung-protective ventilation in ICU patients without ARDS. A strong association, however, exists between country-level economic status and severity-adjusted survival of invasively ventilated patients without ARDS. Further research is needed to identify which factors explain the higher mortality in MICs.

Contributors

LP, AGA, and ASN contributed equally to this study. LP, AGA, ASN, JGL, and MJS designed the meta-analysis. LP, AGA, ASN, TP, and LA harmonised the data from the databases of the studies. ASN had complete access to all data and performed the statistical analyses. LP and MJS drafted this manuscript. All authors critically revised the manuscript and agreed upon submission for publication. All authors had full access to all the data in the study and accept responsibility to submit for publication. ASN and LP have accessed and verified all the data in the study.

Declaration of interests

We declare no competing interests.

Data sharing

A deidentified dataset will be made available upon request to the corresponding author at least 1 year after the publication of this study. The request must include a statistical analysis plan.

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