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PRactice of VENTilation in Middle–Income Countries (PRoVENT–iMIC) – rationale and protocol for a prospective international multicentre observational study in ICUs in Asia

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PRactice of VENTilation in Middle–Income Countries (PRoVENT–iMIC) – rationale and protocol for a prospective international multicentre observational study in ICUs in Asia

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ABSTRACT

Introduction

Current evidence on epidemiology and outcomes of invasively mechanically ventilated intensive care unit (ICU) patients is predominantly gathered in resource–rich settings. Patient case–mixes and patterns of critical illnesses, and probably also ventilation practices are likely to be different in resource–limited settings. We aim to investigate the epidemiological characteristics, ventilation practices and clinical outcomes of patients receiving mechanical ventilation in ICUs in Asia.

Methods and analysis

PRoVENT–iMIC (study of PRactice of VENtilation in Middle Income Countries) is an international multicentre observational study to be undertaken in approximately 60 ICUs in 11 Asian countries. Consecutive patients aged 18 years or older who are receiving invasive ventilation in participating ICUs during a predefined 28–day period are to be enrolled, with a daily follow–up of 7 days. The primary outcome is ventilatory management (including tidal volume [V_T] expressed as mL/kg predicted bodyweight [PBW], and positive end–expiratory pressure [PEEP] expressed as cm H_2O) during the first three days of mechanical ventilation – compared between patients at no risk for ARDS, patients at risk for ARDS and in patients with ARDS (in case the diagnosis of ARDS can be made on admission). Secondary outcomes include occurrence of pulmonary complications and all–cause ICU mortality. The PRoVENT–iMIC study is registered at ClinicalTrials.gov, NCT 03188770.

Ethics and dissemination

PRoVENT–iMIC will be the first international study that prospectively assesses ventilation practices, outcomes and epidemiology of invasively ventilated patients in

ICUs in Asia. The results of this large study, to be disseminated through conference presentations and publications in international peer–reviewed journals, are of ultimate importance when designing trials of invasive ventilation in resource–limited ICUs. Access to source data will be made available through national or international anonymized datasets upon request and after agreement of the PRoVENT–iMIC steering committee.

KEYWORDS: mechanical ventilation; invasive ventilation; ARDS; outcomes; middle–income countries; resource–limited settings.

TRIAL REGISTRATION: PRoVENT–iMIC is registered at www.clinicaltrials.gov with trial identification number NCT 03188770.

STRENGHTS AND LIMITATIONS OF THIS STUDY:

- PRoVENT–iMIC is an international multicentre observational study with a wide representation of Asian countries, allowing inferences on epidemiology, management and outcomes of mechanical ventilation across the entire subcontinent.
- The attention on ventilation practice will provide robust data on this specific domain while the 7 days follow–up will allow precise recording of pulmonary complications at their origin.
- The study will have a sample size large enough to obtain precise estimates of pulmonary complications and ICU mortality and to examine potential associations between ventilation practice and these outcomes.
- One limitation is the potential constraint of laboratory data, generating a limited dataset not comprising daily severity scores useful for statistical controlling purposes.

- The conceivable limitation in blood gas analysis and imaging examinations may limit the documentation of insurgence or worsening of ARDS and other pulmonary complications.

INTRODUCTION

Invasive mechanical ventilation is a frequently applied intervention in patients in intensive care units (ICUs) and a mandatory strategy in patients under general anaesthesia for surgery. There is increased understanding how invasive ventilation can harm the lungs, in ICU patients with the acute respiratory distress syndrome (ARDS) [1], as well as in ICU patients with less injured or uninjured lungs, and in surgery patients who usually have healthy lungs [2]. A central cause is that invasive ventilation with positive pressure may overdistend one lung area while failing to recruit another, compromising gas exchange but also, and more importantly, increasing or inducing pulmonary injury. There is convincing evidence that this harm can be partly prevented by adjusting volume and pressure settings on the ventilator. Indeed, use of low tidal volumes (V_T) [3–5], to prevent overdistension, and sufficient positive end–expiratory pressure (PEEP) [3,5,6], to prevent alveolar collapse or atelectrauma, have both been found to improve outcomes of various types of patients, and their use is increasingly recommended [7–9].

Practice of invasive ventilation has evolved over time, with a more extensive use of ventilator settings that are proven to prevent against so–called ventilator–induced lung injury. The recent LUNG SAFE (‘Large observational study to UNderstand the Global impact of Severe Acute respiratory Failure’) showed that by now up to two in every three patients with ARDS receive so–called lung–protective ventilation[10]. Results of PRoVENT (‘PRactice of VENTilation in critically ill patients without ARDS at onset of ventilation study’) are in line with those from LUNG SAFE, showing that one in every two ICU patients without ARDS receive ventilation with lung–protective settings[11]. Results of LAS VEGAS (‘Local ASsessment of VEntilatory management during General

Anaesthesia for Surgery study') even suggests increased use of lung–protective ventilation in the operating rooms [12]. It should be noticed, though, that LUNG SAFE, PRoVENT, and LAS VEGAS were mainly performed in high–income countries, and exclusively recruiting patients in resource–rich centres, which limits the generalizability of their results to lower–income countries and resource–limited settings. Historical descriptions of cohorts of invasively ventilated patients in resource–poor settings have been published, but these were all small in size, and while suggesting the existence of ventilator–related deaths they largely failed to report key ventilator parameters [13–15]. Continued use of high V_T has been reported in a recent Brazilian study [16], while a study from India suggests a change towards the use of lower V_T [17].

There are several reasons to consider important differences with regard to practice of ventilation between resource–rich and resource–limited settings. The disparity in resources may limit the availability as well as the safety of certain ventilator settings [18]. Awareness of the impact of invasive ventilation on lung tissue, and the benefit of using lung–protective ventilation settings could be severely limited [19]. V_T and PEEP may be poorly titrated due to insufficient staffing, and due to the absence of arterial blood gas monitoring, pulse oximetry or capnography [20]. Other reasons not to implement use of low V_T and sufficient levels of PEEP include alleged side effects associated with their use, like the need for higher respiratory rates, increased sedation requirements, and even the promotion of patient–ventilator asynchrony. As invasive ventilation with higher PEEP may cause hemodynamic instability, limited access to fluids and vasoactive drugs may hamper its use. Finally, as resource–poor ICUs are usually situated in tropical countries their case–mix and indications for invasive ventilation are strikingly different [17].

To gain a better insight into the ventilation practice, outcomes and epidemiological characteristics of ICU patients receiving invasive ventilation in resource–limited settings, we plan to perform the PRoVENT–iMIC ('Practice of VENTilation in Middle–Income Countries study'), a prospective observational cohort study in ICUs in Asia. We also aim to describe the association between certain ventilator settings and patient–centred outcomes. We hypothesize that practice of ventilation is highly variable, in particular with respect to V_T and PEEP settings. This understanding is fundamental to planning any intervention study in these countries in the future.

METHODS and ANALYSIS

Design and Setting

PRoVENT–iMIC is an international multicentre observational study in consecutive ICU patients receiving invasive mechanical ventilation during a 28–day period, expected to run in approximately 60 centres in the following Asian countries: Thailand, Vietnam, Myanmar, Pakistan, Nepal, Bangladesh, Malaysia, Sri Lanka, Maldives, Iran and India. These countries belong to the low or middle–income economies, as classified by the World Bank[21]. PRoVENT–iMIC is conducted in accordance with the declaration of Helsinki and is registered at www.clinicaltrials.gov (trial identification number NCT 03188770). Figure 1 shows the study flow–chart.

Study population

Consecutive patients intubated for ventilation during a predefined period of 28 days will be enrolled. Inclusion is not restricted to patients who are intubated in the ICU: also patients who started invasive ventilation in the emergency room, normal ward, community, or operating room directly preceding the present ICU admission are eligible for participation. The exclusion criteria include age < 18 years, use of non–invasive ventilation not followed by invasive ventilation, patients whose invasive mechanical ventilation started before the 28–day period of inclusion, and patients transferred from another hospital under invasive ventilation.

Patients will be stratified in three groups for comparison of the primary and secondary endpoints: patients without ARDS, patients without but at risk for development of ARDS, according to the Lung Injury Prediction Score (LIPS) [22], and patients with ARDS, according to the Berlin Definition[23]. Patients with ARDS will also

be stratified according to severity of ARDS, based on the oxygenation (mild, moderate and severe ARDS categories).

Study conduct

Local investigators will screen all patients who start invasive ventilation in one of the participating ICUs during a predefined period of 28–day, lasting from 8:00 AM on the Monday of the first week to 7.59 AM on the Monday four weeks later. The exact starting date will be flexible for participating centres and shall be determined by the national study coordinator, but all sites must have started before October 1, 2018.

Data to be collected

Baseline and demographic variables will be collected on the day of admission, including gender, age, actual or estimated weight and height, smoking status, comorbidities including chronic obstructive pulmonary disease (COPD), active cancer, heart failure, diabetes mellitus, chronic kidney failure, liver cirrhosis and arterial hypertension, the presence of ARDS according to the Berlin Definition, the LIPS, reason for ICU admission. On the day of start of invasive ventilation we will document the reason for starting mechanical ventilation, and whether the patient received non-invasive ventilation before intubation.

Every day, until day 3 from admission in the ICU, until ICU discharge or death, whichever comes first, the ventilation status and ventilation characteristics will be collected, including ventilation mode, V_T size, respiratory rate (set and measured), peak and plateau (with volume–controlled modes) or maximum airway pressure (with pressure–controlled modes), PEEP, inspired oxygen fraction, peripheral oxygen saturation, blood gas analysis data when available (PaO_2, $PaCO_2$, arterial bicarbonate,

arterial pH), end–tidal CO_2, when available and hemodynamic parameters like heart rate and systolic blood pressure.

Every day, until day 7, ICU discharge or death, whichever comes first, the occurrence of pulmonary complications will be scored, including new requirement of invasive ventilation after initial extubation, pulmonary infections, atelectasis, pneumothorax, pleural effusions, new pulmonary infiltrates and development or worsening of ARDS.

On the day of ICU discharge (maximum 60 days after recruitment) outcome will be recorded as follows: death, discharge to ward, to medium care or high dependency unit, discharge to home for palliative care, or transfer to another ICU. The date of extubation, reintubation and tracheostomy (if performed) will also be recorded in this moment.

Study endpoints

The primary endpoint is V_T–size in millilitres per kilogram of predicted body weight (ml/kg PBW) and PEEP in centimetres of water (cm H_2O) used amongst diverse ICU patient categories during the first three days of mechanical ventilation. Secondary clinical endpoints include other ventilation parameters (including respiratory system driving pressure), the proportion of patients at risk of ARDS as stratified by the LIPS, or ARDS defined by the Berlin Definition, the occurrence of pulmonary complications, length of stay in ICU, duration of invasive ventilation and all–cause ICU–mortality.

Definitions

All cause ICU–mortality is defined as any death in the ICU. ICU length of stay is defined as the time between ICU admission and ICU discharge or death in ICU. The number of days of ventilation is defined as time between endotracheal intubation and successful

extubation (in case of intermittent mechanical ventilation via a tracheostomy, every day a patient needs ventilation counts as one extra day, irrespective of the duration of ventilation on that specific day). In case of non–invasive ventilation, the duration will be assessed separated from the assessment of invasive ventilation.

Only pulmonary complications that occur after the first 24 hours of invasive ventilation will be considered in analysis, as events preceding this time point may very well be considered the potential reason for intubation. A pulmonary infection requires the presence of new or changed lung opacities on chest radiography and/or new or changed sputum plus at least a temperature > 38.3 °C or a white blood cell count >12,000 per microliter of blood. Atelectasis require the presence of increased density (lung opacity) on one or more chest radiographs with displacement of the fissures toward the area of atelectasis, crowding of pulmonary vessels and bronchi in the atelectatic region, upward displacement of hemidiaphragm ipsilateral to the side of atelectasis, that may be accompanied by shift of the mediastinum or hilum towards the affected area and compensatory overinflation in the unaffected lung [24]. Pleural effusion is suggested by lung opacification with shift of the mediastinum, hilum or hemi–diaphragm towards the non–affected area. Pneumothorax requires the presence of air in the pleural space with no vascular bed surrounding the visceral pleura. ARDS is defined according to the Berlin Definition [23] with alternative oxygenation criteria based on SpO_2/FiO_2 applicable only when blood gas analysis data is unavailable (Table 1a and 1b) [25,26]. Worsening of ARDS is defined as any change in the prior classification (i.e., from mild to moderate or severe ARDS, or from moderate to severe ARDS).

Data management

Data will be collected from a paper medical chart, or an electronic patient data management system if available. Local investigators transcribe the collected data directly onto an anonymized internet–based electronic CRF (REDCap – Research Electronic Data Capture[27], www.projectredcap.org). In some centres data may be recorded on paper CRF and successively transcribed on the electronic CRF at a later time point. Access to the data–entry system is protected by a personalized username and password. The data will be kept on a central secured server located at the Hospital Israelita Albert Einstein, Sao Paulo, Brazil. The structure of the electronic CRF is detailed in Figure 2. A screening–log with limited patient data will be completed with all the included and excluded patients during the enrolment window. Participating centres are instructed to enter data for the daily follow–up using values obtained as close as possible to 08:00 AM, but only when the patient is stable at that time point. The study day for the recording of pulmonary complications will be defined as the natural 24h period from 00:00 until 23:59, to ensure that data is captured only once. Data for ICU–discharge will be collected until a maximum of 60 days after ICU admission, after which the CRF for that patient will be closed.

Study sites

PRoVENT–iMIC will be conducted in 11 Asian countries, with a varying number of ICUs per country. Participating ICUs are selected on the basis of willingness to participate. There are no a priori established requirements for participation, and private as well as public centres are eligible to represent real–life practices. A one–time web–based pre–study survey on structure, organizational aspects and delivery of care in the participating centres will be performed.

Statistical Analysis Plan

No formal sample size calculation was performed, but we expect each centre to enrol 20 to 40 patients in the allocated time period, yielding a total of 1,200 to 2,400 patients. We consider this figure sufficient to analyse the study endpoints.

Normally distributed variables will be expressed by their mean and standard deviation; not normally distributed variables will be expressed by their medians and interquartile ranges; categorical variables will be expressed as n (%). In test groups of continuous normally distributed variables, Student's t-test will be used. Likewise if continuous data are not normally distributed the Mann Whitney U test will be used. Categorical variables will be compared with the Chi-square test or Fisher's exact test or when appropriate as relative risks. Statistical uncertainty will be expressed by 95% confidence levels.

The primary outcome (V_T size [ml/kg PBW] and PEEP [cm H_2O] levels during the first three days of mechanical ventilation) – will be analysed and compared between patients at no risk for ARDS, patients at risk for ARDS and in patients with ARDS (in case the diagnosis of ARDS could be made on admission). If the data is normally distributed, one way Analysis of Variance (ANOVA) or two–way ANOVA assessing the time–interaction between groups and days of observation will be used. When not normally distributed the Kruskal–Wallis test or Friedman test assessing the time–interaction between groups and days of observation will be used.

Univariate analysis will be performed to identify potential factors associated with outcomes including, but not limited to, ventilator settings (in particular V_T and PEEP). A multivariate logistic regression model will be used to determine which of those factors are independent. A stepwise approach will be used to enter new terms into the model,

with a limit of $P < 0.2$ to enter the terms. Time to event variables is analysed using Cox regression and visualized by Kaplan–Meier.

Time–course variables (e.g. repeated measures of ventilator parameters, vital signs, oxygenation parameters and others) are also analysed by linear mixed model. The linear mixed models procedure expands the generalized linear model (GLM) so that the data are permitted to exhibit correlated and non–constant variability.

Pre–specified subgroups in the analyses studying potential associations between ventilator settings and outcome will be: (1) patients at low risk of ARDS vs. patients at risk of ARDS; (2) patients without ARDS vs. patients with ARDS; (3) reason for ICU admission; and (4) reason for start of invasive ventilation. Statistical analyses will be conducted using R (www.r-project.org). A *P*–value of less than 0.05 will be considered statistically significant.

Study organization

The Steering Committee is composed of a selection of PROVE Network investigators plus the national coordinators from each participating country. These investigators were involved in the design of PRoVENT–iMIC. National coordinators are responsible for identifying and recruiting local participating centres. They assist and train the local investigators and oversee the conduct of the study, including administrative management, record keeping and data management. Local investigators in individual participating centres will provide scientific and structural leadership, ensuring local ethical and regulatory approvals are obtained before start of patient inclusion. National Coordinators and Local Investigators are expected to guarantee the quality and security of the data collected.

Prior to start of the study, study teams in each centre will undergo a web–based training session on how to capture data in the electronic CRF. All study team members will be provided with a manual of operations with instructions on how to accurately fill the forms and the screening log. Incomplete or incorrectly entered electronic CRFs will be signalled to the local investigators by the national and international coordinator, for further review of the missing or flagged data.

ETHICS AND DISSEMINATION

The Oxford Tropical Research Ethical Committee (OxTREC) at the University of Oxford, United Kingdom, exempted the study from ethical review on the 2nd of June 2017. Data management, monitoring and reporting of the study will be performed in accordance with the International Conference on Harmonization – Good Clinical Practice guidelines.

All participating centres will also submit the study protocol to the national or local Institutional Review Board for ethical judgment, as applicable by the current regulations in the country. Due to the strict observational design and anonymous collection of data, informed consent may not be required in most countries. However, where informed consent is required, this must be approved by the local ethical committee before the start of inclusion.

The study will be reported following the Strengthening the reporting of Observational Studies in Epidemiology (STROBE) statement guidelines and checklists[28]. The results of this study will be published in a peer–reviewed medical journal. After publication of the primary results, on request the pooled dataset will be available for all members of the PRoVENT–iMIC collaboration for secondary analysis, after judgment and approval of scientific quality and validity of the proposed analysis by the Steering Committee.

DISCUSSION

PRoVENT–iMIC is designed to characterize the epidemiology, ventilator management, occurrence of pulmonary complications and outcomes in invasively ventilated patients in an estimated 60 ICUs in 11 Asian countries. The results of PRoVENT–iMIC will help to understand current ventilation practice in South and Southeast Asia, particularly with respect to variability in ventilator settings amongst patients without, at risk for or with established ARDS. Results of this study will be used to plan future trials of ventilation in ICU patients in these settings.

PRoVENT–iMIC has several strengths. First, we will have a sample size large enough to obtain precise estimates of pulmonary complications and ICU mortality and to examine potential associations between ventilation practice and patient outcomes. Second, the study sample is not restricted to certain patient diagnostic categories. Third, the attention on ventilation practice will provide robust data on this specific domain while the 7 days follow–up will allow precise recording of pulmonary complications at their origin. And finally, the wide representation of Asian countries will allow inferences on geo–economic differences in epidemiology, management and outcomes of mechanical ventilation across the entire subcontinent.

The focus on South and Southeast Asia follows our scarce knowledge about clinical practices and ventilation strategies used in critically ill patients in this and other resource–limited settings [20]. The burden of critical illness in low– and middle–income countries is higher than generally perceived and it is expected to increase with an aging population [29]. Additionally, ICUs are increasingly being set up in the region, especially in busy urban settings. A recent survey highlighted considerable variation in structure, organization and critical care delivery in Asian ICUs, but did not shed light on ventilation

management and patient–centred ventilation–associated outcomes [30]. This information, however, is crucial for future trials of ventilation in ICU patients in these settings, as we need to know whether critically ill patients across Asia equally benefit from lung–protective ventilation as those in Western countries. Additionally, for proper power calculations, information with regard to potential primary endpoints, like the incidence of development of ARDS, duration of ventilation or death, is highly needed. PRoVENT–iMIC will be the first observational study that can provide this information for settings in South Asia. Results restricted to individual settings could also be valuable for local clinicians seeking to improve their local practice, training planning and identify local priorities for quality improvement within their departments.

There is now strong evidence–based support for various ICU process–based interventions such as lung protective ventilation[31], conservative fluid management strategies[32] and weaning protocols[33]. While centre– or country–specific practices or restrictions of resources are potential challenges that affect implementation of all these interventions, we focus on the management of ventilation and especially on the employment of lung–protective ventilation where feasibility may represent an issue specific to resource–limited settings. Recent literature has underlined the potential role of the driving pressure (the pressure amplitude during each artificial breath) and its determinants in the development of ventilator–associated lung injury. Results from PRoVENT–iMIC will provide further data to enable us to discriminate the effects of V_T size, PEEP and driving pressure on outcomes in patients with, at risk of, or without ARDS.

PRoVENT–iMIC will provide important data regarding outcomes following invasive ventilation, including a wide range of clinically important pulmonary

complications. Historical studies from low–resource settings documented mortality rates to exceed 70%[13–15]. However more recent data from South America and India have documented mortality rates of ~40%, similar to that in high–income countries[16,17]. This suggests that mortality in ventilated patients has the potential to improve in low–resource settings[11,12,34]. Although many factors may influence mortality, several underappreciated factors related to invasive ventilation may have contributed, including reduced need for invasive ventilation per se, improvements in safety of invasive ventilation and in liberation from invasive ventilation.

Our interest in patients at risk of ARDS follows a global recent shift in ARDS research. It is now clear that ARDS is rarely present at the time of the initial healthcare encounter, and typically develops during the hospital course, usually between days 2 and 5 in patients with predisposing conditions or risk factors[35]. Hence increasing efforts are being directed toward early identification of patients at risk with a goal of prevention and early treatment prior to the development of a fully established syndrome. This is probably equally important in resource–limited settings where the predisposing conditions and risk modifiers for ARDS may differ and limited escalation of therapy is often the case. PRoVENT–iMIC will be the first study to evaluate prospectively the role of LIPS in these settings. Although the poor predictive accuracy of the LIPS does not currently support its use in everyday clinical practice [36], it has enabled enrolment in clinical trials of ARDS prevention [22] and may yield an initial idea on the patients at risk of and disease progression in the Asian settings under study.

PRoVENT–iMIC has some noticeable shortcomings. The definition of ‘middle–income’ country is rather artificial as the level of health expenditure, local resources and other geo–cultural factors might affect the processes of care in a larger extent than

national income classification. Despite the inclusion of ICUs from 11 countries, which improves study generalizability, caution is needed when applying the results to supposedly similar settings, as substantial intra– and trans–national variations in ICU resources, staffing and organization exist. Second, the case report form used in PRoVENT–iMIC is not exhaustive and does not include data regarding extra–pulmonary complications, hospital–discharge outcomes or other ICU processes of care that may indirectly affect ventilation. Similarly, due to the time window restricted to the ICU stay, we will apply the LIPS at ICU admission and not in the first 6 hours after hospital admission, as originally designed. Mortality may be underestimated in some settings where due to local practices there is the possibility to be discharged home in case of terminal conditions or family decision. To address this we made sure the data collection form captures this event whenever it represents the reason of discharge. Third, due to the limitation of laboratory data we will have a limited dataset that will not comprise daily severity scores useful for statistical controlling purposes. Also, the conceivable limitation in blood gas analysis and radiology exams may limit the documentation of insurgence or worsening of ARDS and other pulmonary complications. Finally, participation in international studies like PRoVENT–iMIC always bears the risk of biased to those centres that do not fully or reliably represent ICU–care in general in the participating countries.

CONLUSIONS

PRoVENT–iMIC is designed to understand the epidemiology, practice of ventilation, and outcomes of critically–ill patients receiving invasive ventilation in a large set of South Asian countries. Results of this study could help identify practices that may best explain differences in outcomes, and could be used in designing new trials of ventilation in these settings.

Author affiliations

Contributors

LP, AGA, ASN, AMD and MJS were equally responsible for writing of the manuscript and participated in study design. FP, PP participated in study design and assisted in writing of the manuscript. AA, AB, KC, AF, RaH, ReH, MH, HAI, KI, SI, GK, BK, HM, BN, RP, SS, LT, SG, NNT, NMY, MGdA reviewed the manuscript and agreed with submission.

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Competing interests

None

Ethics approval

The Oxford Tropical Research Ethical Committee (OxTREC) at the University of Oxford, United Kingdom, exempted the study from ethical review on the 2nd of June 2017. IRB approval was obtained from Sri Lanka, Bangladesh and Malaysia and is underway in Myanmar, Iran, India, Vietnam, Thailand, Nepal, Pakistan and Maldives.

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FIGURE LEGENDS

Figure 1: Flowchart of inclusion of PRoVENT–iMIC

Abbreviations: MV, Mechanical Ventilation; LIPS, Lung Injury Prediction Score; ARDS, Acute Respiratory Distress Syndrome.

Figure 2. Sequence of data submission in the electronic case report form

Abbreviations: LIPS, Lung Injury Prediction Score; MV, mechanical ventilation, ARDS, Acute Respiratory Distress Syndrome; CPE, cardiogenic pulmonary oedema; ICU, Intensive Care Unit.

Figure 1

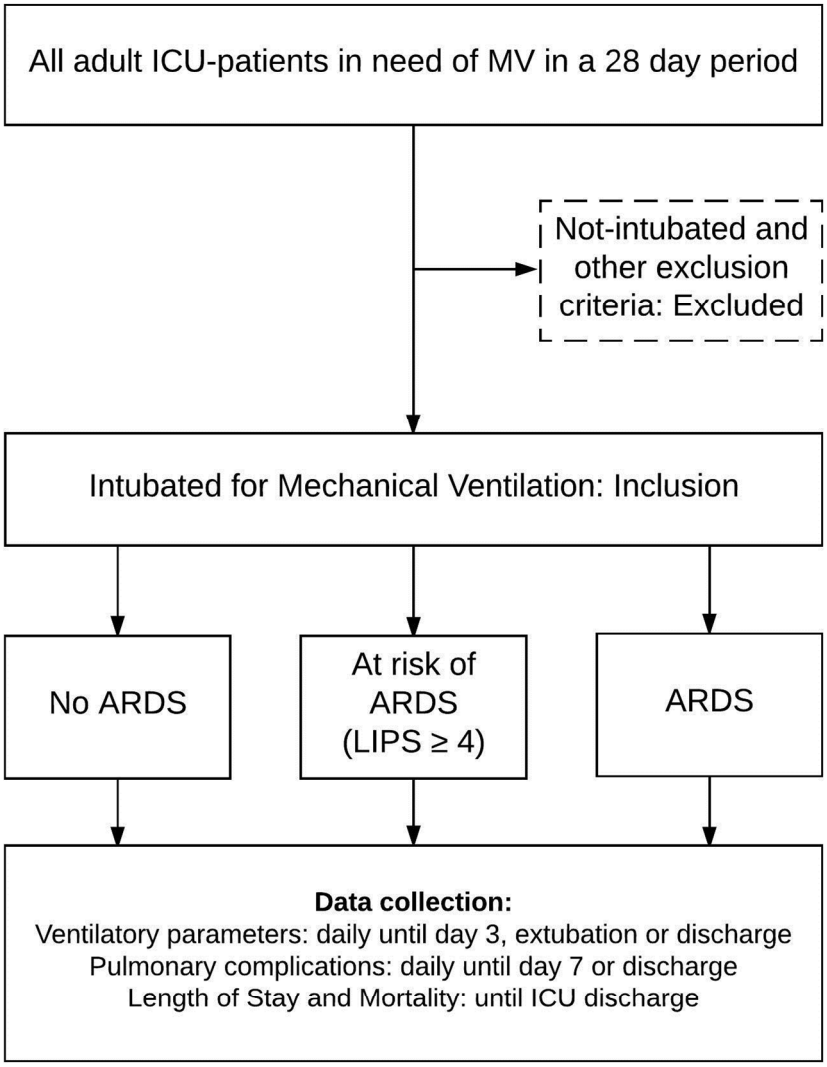

Figure 2

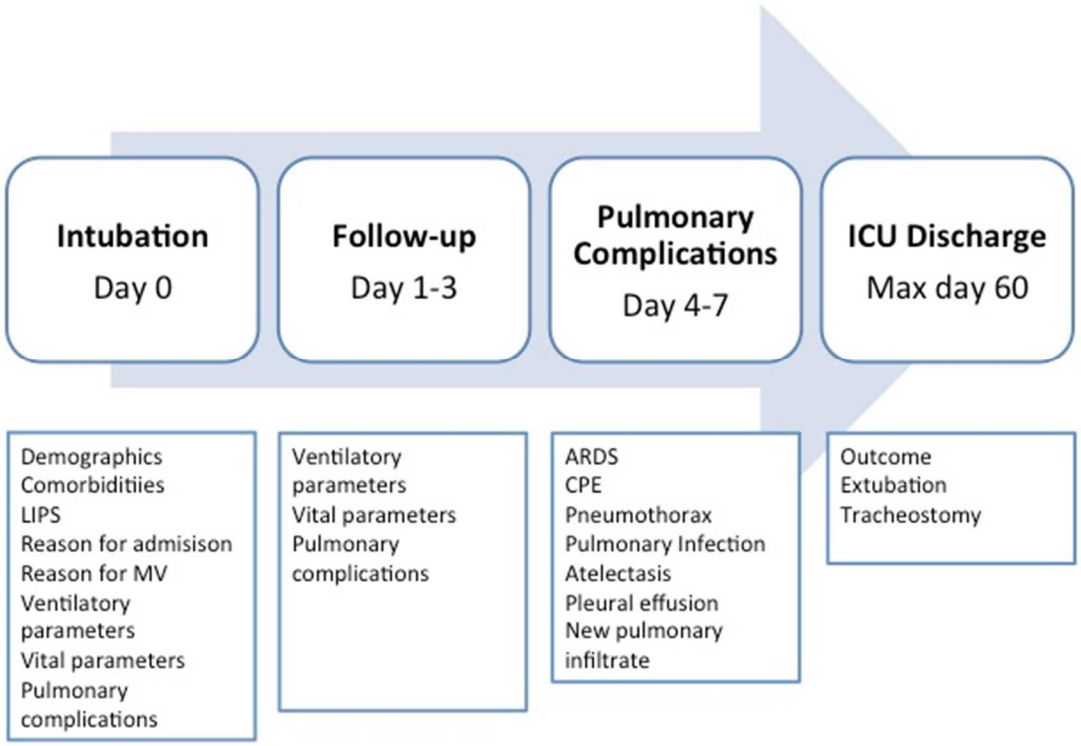

Table 1a. The Berlin definition of ARDS

Criteria	Definition		
Time	Within one week of a known clinical insult, or new/worsening respiratory symptoms		
Chest imaging[1]	Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules		
Origin of oedema	Respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment to exclude hydrostatic oedema if no risk factor present (e.g., echocardiography)		
Oxygenation[2]	Mild	Moderate	Severe
	200<PaO_2/FiO_2≤300 PEEP or CPAP[3] ≥ 5 cm H_2O	100<PaO_2/FiO_2≤ 200 PEEP ≥ 5 cm H_2O	PaO_2/FiO_2 ≤ 100 PEEP ≥ 5 cm H_2O

Abbreviations: ARDS, acute respiratory distress syndrome; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure.
[1]chest X–ray or CT scan; [2]if altitude higher than 1,000 meters, correction factor should be made as follows: PaO_2/FiO_2 x (barometric pressure/760); [3]this may be delivered noninvasively in the mild acute respiratory distress syndrome

Table 1b. Alternative Oxygenation criteria (if PaO_2 data unavailable)

Criteria	Mild ARDS	Moderate ARDS	Severe ARDS
Oxygenation	235<SpO2/FiO2≤315 PEEP or CPAP≥5 cmH2O	150<SpO2/FiO2≤ 235 PEEP ≥ 5 cmH2O	SpO2/FiO2≤ 150 PEEP ≥ 5 cmH2O

Abbreviations: SpO2, pulse oximetry oxygen saturation; FiO2, fraction of inspired oxygen

Table 2. Lung Injury Prediction Score (LIPS) calculation worksheet [17,34]

Predisposing Conditions	Score	Risk Modifiers	Score
Shock	2	Alcohol Abuse	1
Aspiration	2	BMI > 30 kg/m^2	1
Sepsis	1	Hypoalbuminemia	1
Pneumonia	1.5	Chemotherapy	1
High-Risk Surgery		FiO_2 > 0.35 (> 4 l/min)	2
Orthopedic Spine	1	RR > 30 bpm	1.5
Acute Abdomen	2	SpO_2 < 95%	1
Cardiac	2.5	Acidosis (pH < 7.35)	1.5
Aortic Vascular	3.5	Diabetes Mellitus*	- 1
Emergency surgery	1.5		
High-Risk Trauma			
Traumatic Brain Injury	2		
Smoke Inhalation	2		
Near-Drowning	2		
Lung Contusion	1.5		
Multiple Fractures	1.5		

Abbreviations: BMI, body mass index; FiO_2, fraction of inspired oxygen; RR, respiratory Rate; SpO_2, pulse oximetry oxygen saturation.
*(to consider only in septic patients)

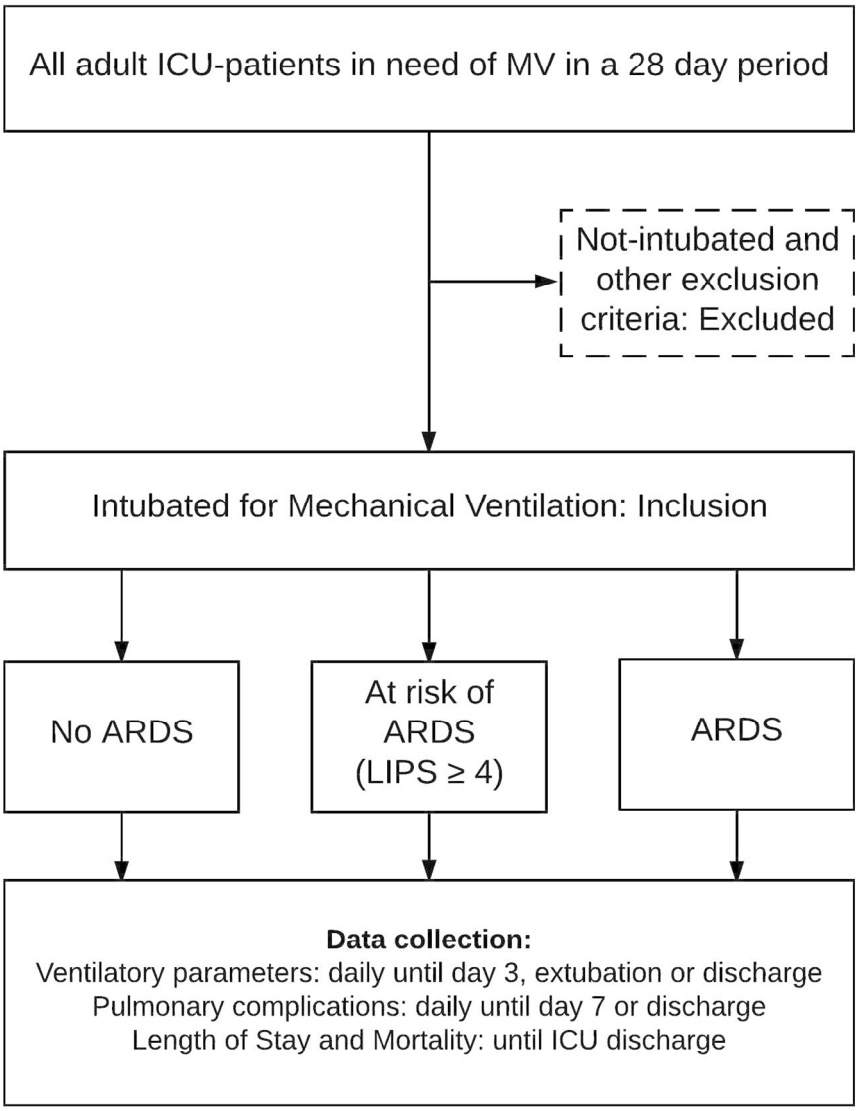

Figure 1: Flowchart of inclusion of PRoVENT–iMIC‼ ┼ . Abbreviations: MV, Mechanical Ventilation; LIPS, Lung Injury Prediction Score; ARDS, Acute Respiratory Distress Syndrome.‼ ┼

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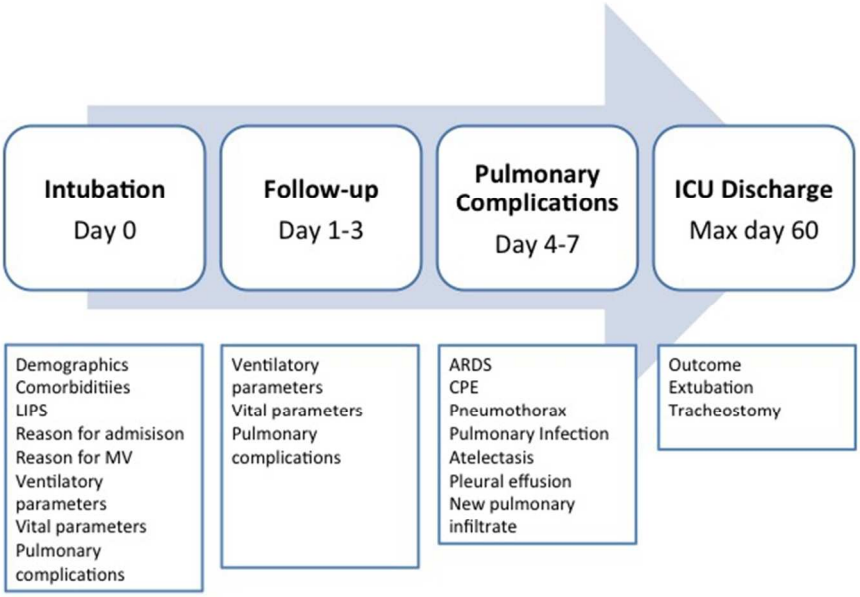

Figure 2: Sequence of data submission in the electronic case report form‼ ┼ . Abbreviations: LIPS, Lung Injury Prediction Score; MV, mechanical ventilation, ARDS, Acute Respiratory Distress Syndrome; CPE, cardiogenic pulmonary oedema; ICU, Intensive Care Unit. ‼ ┼

254x190mm (72 x 72 DPI)

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PRactice of VENTilation in Middle–Income Countries (PRoVENT–iMIC) – rationale and protocol for a prospective international multicentre observational study in intensive care units in Asia

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PRactice of VENTilation in Middle–Income Countries (PRoVENT–iMIC) – rationale and protocol for a prospective international multicentre observational study in Intensive Care Units in Asia

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ABSTRACT

Introduction

Current evidence on epidemiology and outcomes of invasively mechanically ventilated intensive care unit (ICU) patients is predominantly gathered in resource–rich settings. Patient case–mixes and patterns of critical illnesses, and probably also ventilation practices are likely to be different in resource–limited settings. We aim to investigate the epidemiological characteristics, ventilation practices and clinical outcomes of patients receiving mechanical ventilation in ICUs in Asia.

Methods and analysis

PRoVENT–iMIC (study of PRactice of VENtilation in Middle Income Countries) is an international multicentre observational study to be undertaken in approximately 60 ICUs in 11 Asian countries. Consecutive patients aged 18 years or older who are receiving invasive ventilation in participating ICUs during a predefined 28–day period are to be enrolled, with a daily follow–up of 7 days. The primary outcome is ventilatory management (including tidal volume [V_T] expressed as mL/kg predicted bodyweight [PBW], and positive end–expiratory pressure [PEEP] expressed as cm H_2O) during the first three days of mechanical ventilation – compared between patients at no risk for ARDS, patients at risk for ARDS and in patients with ARDS (in case the diagnosis of ARDS can be made on admission). Secondary outcomes include occurrence of pulmonary complications and all–cause ICU mortality. The PRoVENT–iMIC study is registered at ClinicalTrials.gov, NCT 03188770.

Ethics and dissemination

PRoVENT–iMIC will be the first international study that prospectively assesses ventilation practices, outcomes and epidemiology of invasively ventilated patients in

ICUs in Asia. The results of this large study, to be disseminated through conference presentations and publications in international peer–reviewed journals, are of ultimate importance when designing trials of invasive ventilation in resource–limited ICUs. Access to source data will be made available through national or international anonymized datasets upon request and after agreement of the PRoVENT–iMIC steering committee.

KEYWORDS: mechanical ventilation; invasive ventilation; ARDS; outcomes; middle–income countries; resource–limited settings.

TRIAL REGISTRATION: PRoVENT–iMIC is registered at www.clinicaltrials.gov with trial identification number NCT 03188770.

STRENGHTS AND LIMITATIONS OF THIS STUDY:

- PRoVENT–iMIC is an international multicentre observational study with a wide representation of Asian countries, allowing inferences on epidemiology, management and outcomes of mechanical ventilation across the entire subcontinent.
- The attention on ventilation practice will provide robust data on this specific domain while the 7 days follow–up will allow precise recording of pulmonary complications at their origin.
- The study will have a sample size large enough to obtain precise estimates of pulmonary complications and ICU mortality and to examine potential associations between ventilation practice and these outcomes.
- One limitation is the potential constraint of laboratory data, generating a limited dataset not comprising daily severity scores useful for statistical controlling purposes.

- The conceivable limitation in blood gas analysis and imaging examinations may limit the documentation of insurgence or worsening of ARDS and other pulmonary complications.

INTRODUCTION

Invasive mechanical ventilation is a frequently applied intervention in patients in intensive care units (ICUs) and a mandatory strategy in patients under general anaesthesia for surgery. There is increased understanding how invasive ventilation can harm the lungs, in ICU patients with the acute respiratory distress syndrome (ARDS) [1], as well as in ICU patients with less injured or uninjured lungs, and in surgery patients who usually have healthy lungs [2]. A central cause is that invasive ventilation with positive pressure may overdistend one lung area while failing to recruit another, compromising gas exchange but also, and more importantly, increasing or inducing pulmonary injury. There is convincing evidence that this harm can be partly prevented by adjusting volume and pressure settings on the ventilator. Indeed, use of low tidal volumes (V_T) [3–5], to prevent overdistension, and sufficient positive end–expiratory pressure (PEEP) [3,5,6], to prevent alveolar collapse or atelectrauma, have both been found to improve outcomes of various types of patients, and their use is increasingly recommended [7–9]. Furthermore, the driving pressure seems to be another key variable in the development of injury caused by mechanical ventilation, as a large individual patient data metaanalysis showed a clear and consistent association between driving pressure and mortality [10].

Practice of invasive ventilation has evolved over time, with a more extensive use of ventilator settings that are proven to prevent against so–called ventilator–induced lung injury. The recent LUNG SAFE ('Large observational study to UNderstand the Global impact of Severe Acute respiratory Failure') showed that by now up to two in every three patients with ARDS receive so–called lung–protective ventilation[11]. Results of PRoVENT ('PRactice of VENTilation in critically ill patients without ARDS at onset of

ventilation study') are in line with those from LUNG SAFE, showing that one in every two ICU patients without ARDS receive ventilation with lung–protective settings[12]. Results of LAS VEGAS ('Local ASsessment of VEntilatory management during General Anaesthesia for Surgery study') even suggests increased use of lung–protective ventilation in the operating rooms [13]. It should be noticed, though, that LUNG SAFE, PRoVENT, and LAS VEGAS were mainly performed in high–income countries, and exclusively recruiting patients in resource–rich centres, which limits the generalizability of their results to lower–income countries and resource–limited settings. Historical descriptions of cohorts of invasively ventilated patients in resource–poor settings have been published, but these were all small in size, and while suggesting the existence of ventilator–related deaths they largely failed to report key ventilator parameters [14–16]. Continued use of high V_T has been reported in a recent Brazilian study [17], while a study from India suggests a change towards the use of lower V_T [18].

There are several reasons to consider important differences with regard to practice of ventilation between resource–rich and resource–limited settings. The disparity in resources may limit the availability as well as the safety of certain ventilator settings [19]. Awareness of the impact of invasive ventilation on lung tissue, and the benefit of using lung–protective ventilation settings could be severely limited [20]. V_T and PEEP may be poorly titrated due to insufficient staffing, and due to the absence of arterial blood gas monitoring, pulse oximetry or capnography [21]. Other reasons not to implement use of low V_T and sufficient levels of PEEP include alleged side effects associated with their use, like the need for higher respiratory rates, increased sedation requirements, and even the promotion of patient–ventilator asynchrony. As invasive ventilation with higher PEEP may cause hemodynamic instability, limited access to fluids

and vasoactive drugs may hamper its use. Finally, as resource–poor ICUs are usually situated in tropical countries their case–mix and indications for invasive ventilation are strikingly different [18].

To gain a better insight into the ventilation practice, outcomes and epidemiological characteristics of ICU patients receiving invasive ventilation in resource–limited settings, we plan to perform the PRoVENT–iMIC ('Practice of VENTilation in Middle–Income Countries study'), a prospective observational cohort study in ICUs in Asia. We also aim to describe the association between certain ventilator settings and patient–centred outcomes. We hypothesize that practice of ventilation is highly variable, in particular with respect to V_T and PEEP settings. This understanding is fundamental to planning any intervention study in these countries in the future.

METHODS and ANALYSIS

Design and Setting

PRoVENT–iMIC is an international multicentre observational study in consecutive ICU patients receiving invasive mechanical ventilation during a 28–day period, expected to run in approximately 60 centres in the following Asian countries: Thailand, Vietnam, Myanmar, Pakistan, Nepal, Bangladesh, Malaysia, Sri Lanka, Maldives, Iran and India. These countries belong to the low or middle–income economies, as classified by the World Bank [22]. PRoVENT–iMIC is conducted in accordance with the declaration of Helsinki and is registered at www.clinicaltrials.gov (trial identification number NCT 03188770). Figure 1 shows the study flow–chart.

Study population

Consecutive patients intubated for ventilation during a predefined period of 28 days are enrolled. Inclusion is not restricted to patients who are intubated in the ICU, as also patients who started invasive ventilation in the emergency room, normal ward, community, or operating room directly preceding the present ICU admission are eligible for participation, without any minimum or maximum hours of ventilation needed for inclusion. The exclusion criteria include age < 18 years, use of non–invasive ventilation not followed by invasive ventilation, patients whose invasive mechanical ventilation started before the 28–day period of inclusion, and patients transferred from another hospital under invasive ventilation.

Patients will be stratified in three groups for comparison of the primary and secondary endpoints: patients without ARDS, patients without but at risk for development of ARDS, according to the Lung Injury Prediction Score (LIPS, Table 1) [23], and patients with ARDS, according to the Berlin Definition [24]. Patients with ARDS

will also be stratified according to severity of ARDS, based on the oxygenation (mild, moderate and severe ARDS categories).

Study conduct

Local investigators will screen all patients who start invasive ventilation in one of the participating ICUs during a predefined period of 28–day, lasting from 8:00 AM on the Monday of the first week to 7.59 AM on the Monday four weeks later. The exact starting date will be flexible for participating centres and shall be determined by the national study coordinator. Data collection has started in November 2017 in some sites; all sites are expected to initiate the service evaluation within one year after the overall start.

Data to be collected

Baseline and demographic variables will be collected on the day of admission, including gender, age, actual or estimated weight and height, smoking status, comorbidities including chronic obstructive pulmonary disease (COPD), active cancer, heart failure, diabetes mellitus, chronic kidney failure, liver cirrhosis and arterial hypertension, the presence of ARDS according to the Berlin Definition, the LIPS, reason for ICU admission. On the day of start of invasive ventilation we will document the reason for starting mechanical ventilation, and whether the patient received non-invasive ventilation before intubation.

Every day, until day 3 from admission in the ICU, until ICU discharge or death, whichever comes first, the ventilation status and ventilation characteristics will be collected, including ventilation mode, V_T size, respiratory rate (set and measured), peak and plateau pressure, PEEP, inspired oxygen fraction, peripheral oxygen saturation, blood gas analysis data when available (PaO_2, $PaCO_2$, arterial bicarbonate, arterial pH),

end–tidal CO_2, when available and hemodynamic parameters like heart rate and systolic blood pressure.

Every day, until day 7, ICU discharge or death, whichever comes first, the occurrence of pulmonary complications will be scored, including new requirement of invasive ventilation after initial extubation, pulmonary infections, atelectasis, pneumothorax, pleural effusions, new pulmonary infiltrates and development or worsening of ARDS.

On the day of ICU discharge (maximum 60 days after recruitment) outcome will be recorded as follows: death, discharge to ward, to medium care or high dependency unit, discharge to home for palliative care, or transfer to another ICU. The date of extubation, reintubation and tracheostomy (if performed) will also be recorded in this moment.

Study endpoints

The primary endpoint is V_T–size in millilitres per kilogram of predicted body weight (ml/kg PBW) and PEEP in centimetres of water (cm H_2O) used amongst diverse ICU patient categories during the first three days of mechanical ventilation. Secondary clinical endpoints include other ventilation parameters (including respiratory system driving pressure, the proportion of patients at risk of ARDS as stratified by the LIPS, or ARDS defined by the Berlin Definition, the occurrence of pulmonary complications, length of stay in ICU, duration of invasive ventilation and all–cause ICU–mortality.

Definitions

All cause ICU–mortality is defined as any death in the ICU. ICU length of stay is defined as the time between ICU admission and ICU discharge or death in ICU. The number of days of ventilation is defined as time between endotracheal intubation and successful

extubation (in case of intermittent mechanical ventilation via a tracheostomy, every day a patient needs ventilation counts as one extra day, irrespective of the duration of ventilation on that specific day). In case of non–invasive ventilation, the duration will be assessed separated from the assessment of invasive ventilation. The presence of spontaneous activity will be identified by any recorded difference between the set and measured respiratory rate.

Driving pressure will be calculated by subtracting the level of PEEP from the plateau pressure (Pplat in volume–control ventilation) or maximal airway pressure (Pmax in pressure control ventilation). Pplat and Pmax are considered reliable for this calculation if the patient is receiving complete ventilatory assistance without evidence of spontaneous activity, i.e., only when the set respiratory rate equals the measured respiratory rate. Peak airways pressures will not be used to compute driving pressure as these represent a poor surrogate of the plateau pressure. Only pulmonary complications that occur after the first 24 hours of invasive ventilation will be considered in analysis, as events preceding this time point may very well be considered the potential reason for intubation. A pulmonary infection requires the presence of new or changed lung opacities on chest radiography and/or new or changed sputum plus at least a temperature > 38.3 °C or a white blood cell count >12,000 per microliter of blood. Atelectasis require the presence of increased density (lung opacity) on one or more chest radiographs with displacement of the fissures toward the area of atelectasis, crowding of pulmonary vessels and bronchi in the atelectatic region, upward displacement of hemidiaphragm ipsilateral to the side of atelectasis, that may be accompanied by shift of the mediastinum or hilum towards the affected area and compensatory overinflation in the unaffected lung [25]. Pleural effusion is suggested by

lung opacification with shift of the mediastinum, hilum or hemi–diaphragm towards the non–affected area. Pneumothorax requires the presence of air in the pleural space with no vascular bed surrounding the visceral pleura. ARDS is defined according to the Berlin Definition [24] with alternative oxygenation criteria based on SpO_2/FiO_2 applicable only when blood gas analysis data is unavailable (Table 2a and 2b) [26,27]. Worsening of ARDS is defined as any change in the prior classification (i.e., from mild to moderate or severe ARDS, or from moderate to severe ARDS).

Data management

Data will be collected from a paper medical chart, or an electronic patient data management system if available. Local investigators transcribe the collected data directly onto an anonymized internet–based electronic CRF (REDCap – Research Electronic Data Capture [28], www.projectredcap.org). In some centres data may be recorded on paper CRF and successively transcribed on the electronic CRF at a later time point. Access to the data–entry system is protected by a personalized username and password. The data will be kept on a central secured server located at the Hospital Israelita Albert Einstein, Sao Paulo, Brazil. The structure of the electronic CRF is detailed in Figure 2. A screening–log with limited patient data will be completed with all the included and excluded patients during the enrolment window. Participating centres are instructed to enter data for the daily follow–up using values obtained as close as possible to 08:00 AM, but only when the patient is stable at that time point. The study day for the recording of pulmonary complications will be defined as the natural 24h period from 00:00 until 23:59, to ensure that data is captured only once. Data for ICU–discharge will be collected until a maximum of 60 days after ICU admission, after which the CRF for that patient will be closed.

Study sites

PRoVENT–iMIC will be conducted in 11 Asian countries, with a varying number of ICUs per country. Participating ICUs are selected on the basis of willingness to participate. There are no a priori established requirements for participation, and private as well as public centres are eligible to represent real–life practices. A one–time web–based pre–study survey on structure, organizational aspects and delivery of care in the participating centres will be performed. Each participating centre is surveyed once regarding the following information: hospital characteristics (private vs. public), ICU characteristics (medical vs. surgical vs. mixed, and open vs. closed, number of ICU beds, annual number of patient admitted, number of ventilators available, and other organ support measures), and staffing (nurse to patient ratio, physician to patient ratio, presence of specialized medical staff, and overnight coverage).

Statistical Analysis Plan

No formal sample size calculation was performed, but we expect each centre to enrol 20 to 40 patients in the allocated time period, yielding a total of 1,200 to 2,400 patients. We consider this figure sufficient to analyse the study endpoints.

Normally distributed variables will be expressed by their mean and standard deviation; not normally distributed variables will be expressed by their medians and interquartile ranges; categorical variables will be expressed as n (%). In test groups of continuous normally distributed variables, Student's t-test will be used. Likewise if continuous data are not normally distributed the Mann Whitney U test will be used. Categorical variables will be compared with the Chi-square test or Fisher's exact test or when appropriate as relative risks. Statistical uncertainty will be expressed by 95% confidence levels.

The primary outcome (V_T size [ml/kg PBW] and PEEP [cm H_2O] levels during the first three days of mechanical ventilation) – will be analysed and compared between patients at no risk for ARDS, patients at risk for ARDS and in patients with ARDS (in case the diagnosis of ARDS could be made on admission). If the data is normally distributed, one way Analysis of Variance (ANOVA) or two–way ANOVA assessing the time–interaction between groups and days of observation will be used. When not normally distributed the Kruskal–Wallis test or Friedman test assessing the time–interaction between groups and days of observation will be used.

Univariate analysis will be performed to identify potential factors associated with outcomes including, but not limited to, ventilator settings (in particular V_T and PEEP). A multivariate logistic regression model will be used to determine which of those factors are independent. A stepwise approach will be used to enter new terms into the model, with a limit of $P < 0.2$ to enter the terms. Time to event variables is analysed using Cox regression and visualized by Kaplan–Meier.

Time–course variables (e.g. repeated measures of ventilator parameters, vital signs, oxygenation parameters and others) are also analysed by linear mixed model. The linear mixed models procedure expands the generalized linear model (GLM) so that the data are permitted to exhibit correlated and non–constant variability.

Pre–specified subgroups in the analyses studying potential associations between ventilator settings and outcome will be: (1) patients at low risk of ARDS vs. patients at risk of ARDS; (2) patients without ARDS vs. patients with ARDS; (3) reason for ICU admission; and (4) reason for start of invasive ventilation. Statistical analyses will be conducted using R (www.r-project.org). A *P*–value of less than 0.05 will be considered statistically significant.

Study organization

The Steering Committee is composed of a selection of PROVE Network investigators plus the national coordinators from each participating country. These investigators were involved in the design of PRoVENT–iMIC. National coordinators are responsible for identifying and recruiting local participating centres. They assist and train the local investigators and oversee the conduct of the study, including administrative management, record keeping and data management. Local investigators in individual participating centres will provide scientific and structural leadership, ensuring local ethical and regulatory approvals are obtained before start of patient inclusion. National Coordinators and Local Investigators are expected to guarantee the quality and security of the data collected.

Prior to start of the study, study teams in each centre will undergo a web–based training session on how to capture data in the electronic CRF. All study team members will be provided with a manual of operations with instructions on how to accurately fill the forms and the screening log. Incomplete or incorrectly entered electronic CRFs will be signalled to the local investigators by the national and international coordinator, for further review of the missing or flagged data.

ETHICS AND DISSEMINATION

The Oxford Tropical Research Ethical Committee (OxTREC) at the University of Oxford, United Kingdom, exempted the study from ethical review on the 9th of June 2017. Data management, monitoring and reporting of the study will be performed in accordance with the International Conference on Harmonization – Good Clinical Practice guidelines.

All participating centres will also submit the study protocol to the national or local Institutional Review Board for ethical judgment, as applicable by the current regulations in the country. Due to the strict observational design and anonymous collection of data, informed consent may not be required in most countries. However, where informed consent is required, this must be approved by the local ethical committee before the start of inclusion.

The study will be reported following the Strengthening the reporting of Observational Studies in Epidemiology (STROBE) statement guidelines and checklists [29]. The results of this study will be published in a peer–reviewed medical journal. After publication of the primary results, on request the pooled dataset will be available for all members of the PRoVENT–iMIC collaboration for secondary analysis, after judgment and approval of scientific quality and validity of the proposed analysis by the Steering Committee.

DISCUSSION

PRoVENT–iMIC is designed to characterize the epidemiology, ventilator management, occurrence of pulmonary complications and outcomes in invasively ventilated patients in an estimated 60 ICUs in 11 Asian countries. The results of PRoVENT–iMIC will help to understand current ventilation practice in South and Southeast Asia, particularly with respect to variability in ventilator settings amongst patients without, at risk for or with established ARDS. Results of this study will be used to plan future trials of ventilation in ICU patients in these settings.

PRoVENT–iMIC has several strengths. First, its prospective design will allow a higher accuracy of data capturing with regard to exposures, confounders and endpoints compared to studies that used a retrospective design [30]. While a prospective design may cause sources of bias or establish causal effects, it minimizes the chance of residual confounding by unmeasured variables, a common limitation with a retrospective design, as has frequently been used in mechanical ventilation epidemiological studies [31–33]. We will have a sample size large enough to obtain precise estimates of pulmonary complications and ICU mortality and to examine potential associations between ventilation practice and patient outcomes. Second, the study sample is not restricted to certain patient diagnostic categories. Third, the attention on ventilation practice will provide robust data on this specific domain while the 7 days follow–up will allow precise recording of pulmonary complications at their origin. And finally, the wide representation of Asian countries will allow inferences on geo–economic differences in epidemiology, management and outcomes of mechanical ventilation across the entire subcontinent.

The focus on South and Southeast Asia follows our scarce knowledge about clinical practices and ventilation strategies used in critically ill patients in this and other resource–limited settings [21]. The burden of critical illness in low– and middle–income countries is higher than generally perceived and it is expected to increase with an aging population [34]. Additionally, ICUs are increasingly being set up in the region, especially in busy urban settings. A recent survey highlighted considerable variation in structure, organization and critical care delivery in Asian ICUs, but did not shed light on ventilation management and patient–centred ventilation–associated outcomes [35]. This information, however, is crucial for future trials of ventilation in ICU patients in these settings, as we need to know whether critically ill patients across Asia equally benefit from lung–protective ventilation as those in Western countries. Additionally, for proper power calculations, information with regard to potential primary endpoints, like the incidence of development of ARDS, duration of ventilation or death, is highly needed. PRoVENT–iMIC will be the first observational study that can provide this information for settings in South Asia. Results restricted to individual settings could also be valuable for local clinicians seeking to improve their local practice, training planning and identify local priorities for quality improvement within their departments.

There is now strong evidence–based support for various ICU process–based interventions such as lung protective ventilation[36], conservative fluid management strategies[37] and weaning protocols [38]. While centre– or country–specific practices or restrictions of resources are potential challenges that affect implementation of all these interventions, we focus on the management of ventilation and especially on the employment of lung–protective ventilation where feasibility may represent an issue specific to resource–limited settings. Recent literature has underlined the potential role

of the driving pressure (the pressure amplitude during each artificial breath) and its determinants in the development of ventilator–associated lung injury. Results from PRoVENT–iMIC will provide further data to enable us to discriminate the effects of V_T size, PEEP and driving pressure on outcomes in patients with, at risk of, or without ARDS.

PRoVENT–iMIC will provide important data regarding outcomes following invasive ventilation, including a wide range of clinically important pulmonary complications. Historical studies from low–resource settings documented mortality rates to exceed 70% [14–16]. However more recent data from South America and India have documented mortality rates of ~40%, similar to that in high–income countries[17,18]. This suggests that mortality in ventilated patients has the potential to improve in low–resource settings [12,13,39]. Although many factors may influence mortality, several underappreciated factors related to invasive ventilation may have contributed, including reduced need for invasive ventilation per se, improvements in safety of invasive ventilation and in liberation from invasive ventilation.

Our interest in patients at risk of ARDS follows a global recent shift in ARDS research. It is now clear that ARDS is rarely present at the time of the initial healthcare encounter, and typically develops during the hospital course, usually between days 2 and 5 in patients with predisposing conditions or risk factors [40]. Hence increasing efforts are being directed toward early identification of patients at risk with a goal of prevention and early treatment prior to the development of a fully established syndrome. This is probably equally important in resource–limited settings where the predisposing conditions and risk modifiers for ARDS may differ and limited escalation of therapy is often the case. PRoVENT–iMIC will be the first study to evaluate prospectively the role

of LIPS in these settings. Although the poor predictive accuracy of the LIPS does not currently support its use in everyday clinical practice [41], it has enabled enrolment in clinical trials of ARDS prevention [23] and may yield an initial idea on the patients at risk of and disease progression in the Asian settings under study.

PRoVENT–iMIC has some noticeable shortcomings. The definition of 'middle–income' country is rather artificial as the level of health expenditure, local resources and other geo–cultural factors might affect the processes of care in a larger extent than national income classification. Despite the inclusion of ICUs from 11 countries, which improves study generalizability, caution is needed when applying the results to supposedly similar settings, as substantial intra– and trans–national variations in ICU resources, staffing and organization exist. Second, the case report form used in PRoVENT–iMIC was designed so that it would not induce excessive work–load for the participating centres. Therefore, we decided not to collect data regarding extra–pulmonary complications and hospital–discharge outcomes, neither the amounts of sedation used and sedation levels. Similarly, due to the time window restricted to the ICU stay, we will apply the LIPS at ICU admission and not in the first 6 hours after hospital admission, as originally designed. Mortality may be underestimated in some settings where due to local practices there is the possibility to be discharged home in case of terminal conditions or family decision. To address this we made sure the data collection form captures this event whenever it represents the reason of discharge. Third, due to the limitation of laboratory data we will have a limited dataset that will not comprise daily severity scores useful for statistical controlling purposes. Also, the conceivable limitation in blood gas analysis and radiology exams may limit the documentation of insurgence or worsening of ARDS and other pulmonary complications.

Finally, we cannot exclude that ventilator settings applied by treating physicians might be biased by the participation in the study, a problem that also existed in prior multinational studies [11,12]. Also participation in international studies like PRoVENT–iMIC always bears the risk of biased to those centres that do not fully or reliably represent ICU–care in general in the participating countries.

CONLUSIONS

PRoVENT–iMIC is designed to understand the epidemiology, practice of ventilation, and outcomes of critically–ill patients receiving invasive ventilation in a large set of South Asian countries. Results of this study could help identify practices that may best explain differences in outcomes, and could be used in designing new trials of ventilation in these settings.

Author affiliations

Contributors

LP, AGA, ASN, AMD and MJS were equally responsible for writing of the manuscript and participated in study design. FP, PP participated in study design and assisted in writing of the manuscript. AA, AB, KC, AF, RaH, ReH, MH, HAI, KI, SI, GK, BK, HM, BN, RP, SS, LT, SG, NNT, NMY, MGdA reviewed the manuscript and agreed with submission.

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Competing interests

None

Ethics approval

The Oxford Tropical Research Ethical Committee (OxTREC) at the University of Oxford, United Kingdom, exempted the study from ethical review on the 9th of June 2017. IRB approval was obtained from Sri Lanka, Bangladesh and Malaysia and is underway in Myanmar, Iran, India, Vietnam, Thailand, Nepal, Pakistan and Maldives.

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FIGURE LEGENDS

Figure 1: Flowchart of inclusion of PRoVENT–iMIC

Abbreviations: MV, Mechanical Ventilation; LIPS, Lung Injury Prediction Score; ARDS, Acute Respiratory Distress Syndrome.

Figure 2. Sequence of data submission in the electronic case report form

Abbreviations: LIPS, Lung Injury Prediction Score; MV, mechanical ventilation, ARDS, Acute Respiratory Distress Syndrome; CPE, cardiogenic pulmonary oedema; ICU, Intensive Care Unit.

Table 1. Lung Injury Prediction Score (LIPS) calculation worksheet [17,34]

Predisposing Conditions	Score	Risk Modifiers	Score
Shock	2	Alcohol Abuse	1
Aspiration	2	BMI > 30 kg/m^2	1
Sepsis	1	Hypoalbuminemia	1
Pneumonia	1.5	Chemotherapy	1
High-Risk Surgery		FiO_2 > 0.35 (> 4 l/min)	2
Orthopedic Spine	1	RR > 30 bpm	1.5
Acute Abdomen	2	SpO_2 < 95%	1
Cardiac	2.5	Acidosis (pH < 7.35)	1.5
Aortic Vascular	3.5	Diabetes Mellitus*	- 1
Emergency surgery	1.5		
High-Risk Trauma			
Traumatic Brain Injury	2		
Smoke Inhalation	2		
Near-Drowning	2		
Lung Contusion	1.5		
Multiple Fractures	1.5		

Abbreviations: BMI, body mass index; FiO_2, fraction of inspired oxygen; RR, respiratory rate; SpO_2, pulse oximetry oxygen saturation.
*(To consider only in septic patients)

Table 2a. The Berlin definition of ARDS

Criteria	Definition		
Time	Within one week of a known clinical insult, or new/worsening respiratory symptoms		
Chest imaging[1]	Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules		
Origin of oedema	Respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment to exclude hydrostatic oedema if no risk factor present (e.g., echocardiography)		
Oxygenation[2]	Mild	Moderate	Severe
	$200<PaO_2/FiO_2 \leq 300$	$100<PaO_2/FiO_2 \leq 200$	$PaO_2/FiO_2 \leq 100$
	PEEP or CPAP[3] ≥ 5 cm H_2O	PEEP ≥ 5 cm H_2O	PEEP ≥ 5 cm H_2O

Abbreviations: ARDS, acute respiratory distress syndrome; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure.
[1]chest X–ray or CT scan; [2]if altitude higher than 1,000 meters, correction factor should be made as follows: PaO_2/FiO_2 x (barometric pressure/760); [3]this may be delivered noninvasively in the mild acute respiratory distress syndrome

Table 2b. Alternative Oxygenation criteria (if PaO_2 data unavailable)

Criteria	Mild ARDS	Moderate ARDS	Severe ARDS
Oxygenation	$235<SpO_2/FiO_2 \leq 315$	$150<SpO_2/FiO_2 \leq 235$	$SpO_2/FiO_2 \leq 150$
	PEEP or CPAP≥5 cmH2O	PEEP ≥ 5 cmH2O	PEEP ≥ 5 cmH2O

Abbreviations: SpO2, pulse oximetry oxygen saturation; FiO2, fraction of inspired oxygen

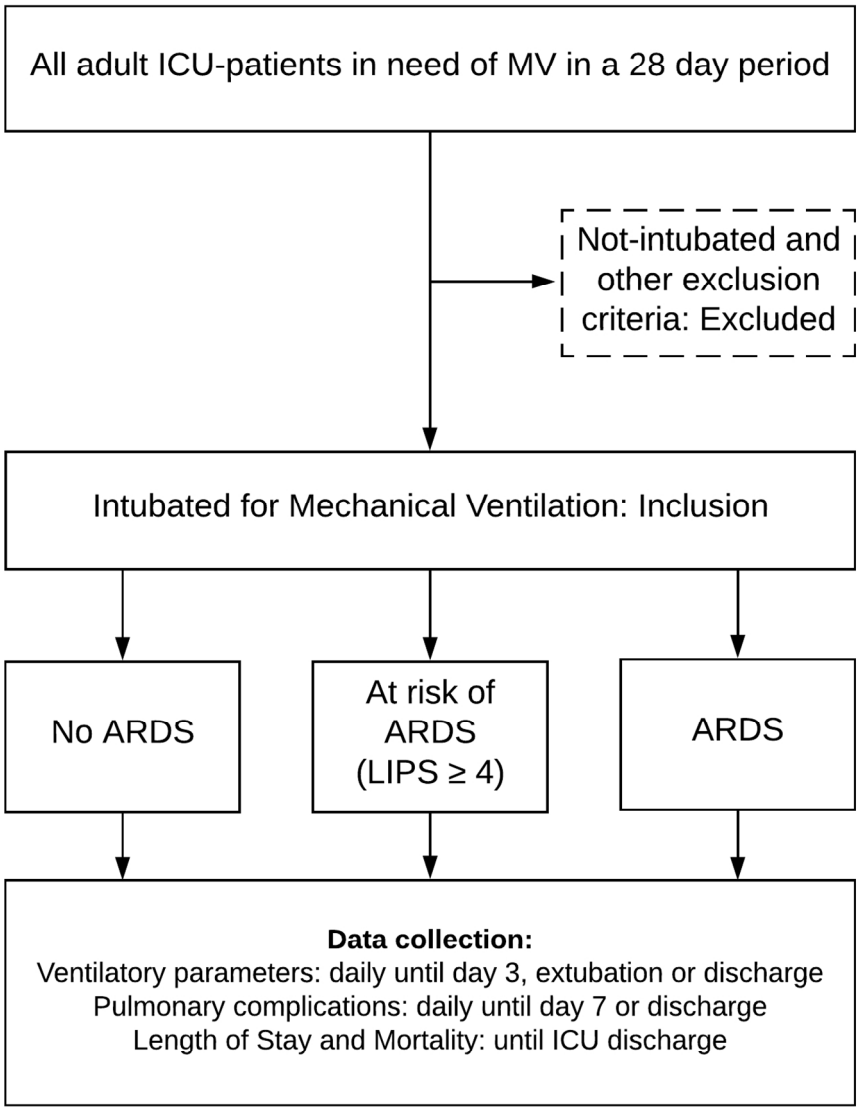

Figure 1. Flowchart of inclusion of PRoVENT–iMIC. Abbreviations: MV, Mechanical Ventilation; LIPS, Lung Injury Prediction Score; ARDS, Acute Respiratory Distress Syndrome.

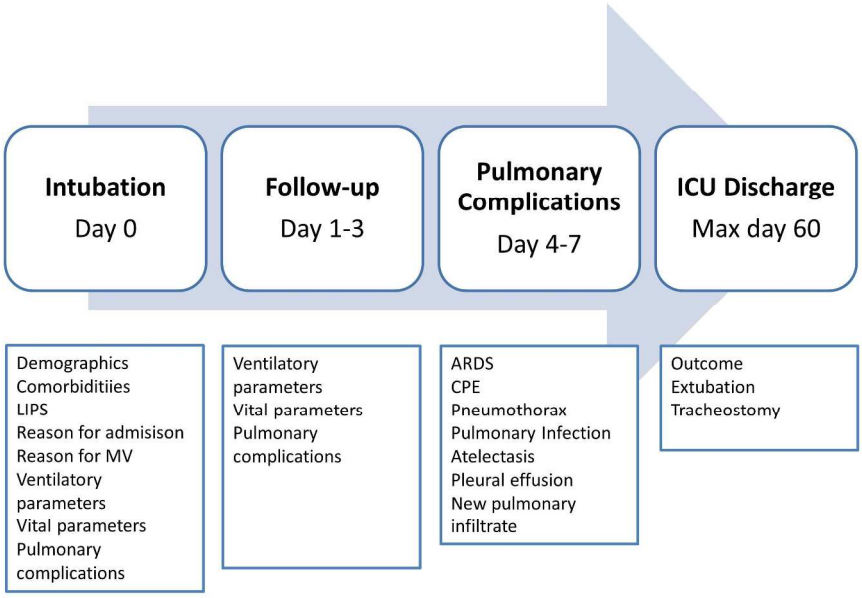

Figure 2. Sequence of data submission in the electronic case report form‼ ┼ . Abbreviations: LIPS, Lung Injury Prediction Score; MV, mechanical ventilation, ARDS, Acute Respiratory Distress Syndrome; CPE, cardiogenic pulmonary oedema; ICU, Intensive Care Unit. ‼ ┼

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PRactice of VENTilation in Middle–Income Countries (PRoVENT–iMIC) – rationale and protocol for a prospective international multicentre observational study in intensive care units in Asia

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PRactice of VENTilation in Middle–Income Countries (PRoVENT–iMIC) – rationale and protocol for a prospective international multicentre observational study in Intensive Care Units in Asia

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ABSTRACT

Introduction

Current evidence on epidemiology and outcomes of invasively mechanically ventilated intensive care unit (ICU) patients is predominantly gathered in resource–rich settings. Patient case–mixes and patterns of critical illnesses, and probably also ventilation practices are likely to be different in resource–limited settings. We aim to investigate the epidemiological characteristics, ventilation practices and clinical outcomes of patients receiving mechanical ventilation in ICUs in Asia.

Methods and analysis

PRoVENT–iMIC (study of PRactice of VENtilation in Middle Income Countries) is an international multicentre observational study to be undertaken in approximately 60 ICUs in 11 Asian countries. Consecutive patients aged 18 years or older who are receiving invasive ventilation in participating ICUs during a predefined 28–day period are to be enrolled, with a daily follow–up of 7 days. The primary outcome is ventilatory management (including tidal volume [V_T] expressed as mL/kg predicted bodyweight [PBW], and positive end–expiratory pressure [PEEP] expressed as cm H_2O) during the first three days of mechanical ventilation – compared between patients at no risk for ARDS, patients at risk for ARDS and in patients with ARDS (in case the diagnosis of ARDS can be made on admission). Secondary outcomes include occurrence of pulmonary complications and all–cause ICU mortality. The PRoVENT–iMIC study is registered at ClinicalTrials.gov, NCT 03188770.

Ethics and dissemination

PRoVENT–iMIC will be the first international study that prospectively assesses ventilation practices, outcomes and epidemiology of invasively ventilated patients in

ICUs in Asia. The results of this large study, to be disseminated through conference presentations and publications in international peer–reviewed journals, are of ultimate importance when designing trials of invasive ventilation in resource–limited ICUs. Access to source data will be made available through national or international anonymized datasets upon request and after agreement of the PRoVENT–iMIC steering committee.

KEYWORDS: mechanical ventilation; invasive ventilation; ARDS; outcomes; middle–income countries; resource–limited settings.

TRIAL REGISTRATION: PRoVENT–iMIC is registered at www.clinicaltrials.gov with trial identification number NCT 03188770.

STRENGHTS AND LIMITATIONS OF THIS STUDY:

- PRoVENT–iMIC is an international multicentre observational study with a wide representation of Asian countries, allowing inferences on epidemiology, management and outcomes of mechanical ventilation across the entire subcontinent.
- The attention on ventilation practice will provide robust data on this specific domain while the 7 days follow–up will allow precise recording of pulmonary complications at their origin.
- The study will have a sample size large enough to obtain precise estimates of pulmonary complications and ICU mortality and to examine potential associations between ventilation practice and these outcomes.
- One limitation is the potential constraint of laboratory data, generating a limited dataset not comprising daily severity scores useful for statistical controlling purposes.

- The conceivable limitation in blood gas analysis and imaging examinations may limit the documentation of insurgence or worsening of ARDS and other pulmonary complications.

INTRODUCTION

Invasive mechanical ventilation is a frequently applied intervention in patients in intensive care units (ICUs) and a mandatory strategy in patients under general anaesthesia for surgery. There is increased understanding how invasive ventilation can harm the lungs, in ICU patients with the acute respiratory distress syndrome (ARDS) [1], as well as in ICU patients with less injured or uninjured lungs, and in surgery patients who usually have healthy lungs [2]. A central cause is that invasive ventilation with positive pressure may overdistend one lung area while failing to recruit another, compromising gas exchange but also, and more importantly, increasing or inducing pulmonary injury. There is convincing evidence that this harm can be partly prevented by adjusting volume and pressure settings on the ventilator. Indeed, use of low tidal volumes (V_T) [3–5], to prevent overdistension, and sufficient positive end–expiratory pressure (PEEP) [3,5,6], to prevent alveolar collapse or atelectrauma, have both been found to improve outcomes of various types of patients, and their use is increasingly recommended [7–9]. Furthermore, the driving pressure seems to be another key variable in the development of injury caused by mechanical ventilation, as a large individual patient data metaanalysis showed a clear and consistent association between driving pressure and mortality [10].

Practice of invasive ventilation has evolved over time, with a more extensive use of ventilator settings that are proven to prevent against so–called ventilator–induced lung injury. The recent LUNG SAFE ('Large observational study to UNderstand the Global impact of Severe Acute respiratory Failure') showed that by now up to two in every three patients with ARDS receive so–called lung–protective ventilation[11]. Results of PRoVENT ('PRactice of VENTilation in critically ill patients without ARDS at onset of

ventilation study') are in line with those from LUNG SAFE, showing that one in every two ICU patients without ARDS receive ventilation with lung–protective settings[12]. Results of LAS VEGAS ('Local ASsessment of VEntilatory management during General Anaesthesia for Surgery study') even suggests increased use of lung–protective ventilation in the operating rooms [13]. It should be noticed, though, that LUNG SAFE, PRoVENT, and LAS VEGAS were mainly performed in high–income countries, and exclusively recruiting patients in resource–rich centres, which limits the generalizability of their results to lower–income countries and resource–limited settings. Historical descriptions of cohorts of invasively ventilated patients in resource–poor settings have been published, but these were all small in size, and while suggesting the existence of ventilator–related deaths they largely failed to report key ventilator parameters [14–16]. Continued use of high V_T has been reported in a recent Brazilian study [17], while a study from India suggests a change towards the use of lower V_T [18].

There are several reasons to consider important differences with regard to practice of ventilation between resource–rich and resource–limited settings. The disparity in resources may limit the availability as well as the safety of certain ventilator settings [19]. Awareness of the impact of invasive ventilation on lung tissue, and the benefit of using lung–protective ventilation settings could be severely limited [20]. V_T and PEEP may be poorly titrated due to insufficient staffing, and due to the absence of arterial blood gas monitoring, pulse oximetry or capnography [21]. Other reasons not to implement use of low V_T and sufficient levels of PEEP include alleged side effects associated with their use, like the need for higher respiratory rates, increased sedation requirements, and even the promotion of patient–ventilator asynchrony. As invasive ventilation with higher PEEP may cause hemodynamic instability, limited access to fluids

and vasoactive drugs may hamper its use. Finally, as resource–poor ICUs are usually situated in tropical countries their case–mix and indications for invasive ventilation are strikingly different [18].

To gain a better insight into the ventilation practice, outcomes and epidemiological characteristics of ICU patients receiving invasive ventilation in resource–limited settings, we plan to perform the PRoVENT–iMIC ('Practice of VENTilation in Middle–Income Countries study'), a prospective observational cohort study in ICUs in Asia. We also aim to describe the association between certain ventilator settings and patient–centred outcomes. We hypothesize that practice of ventilation is highly variable, in particular with respect to V_T and PEEP settings. This understanding is fundamental to planning any intervention study in these countries in the future.

METHODS and ANALYSIS

Design and Setting

PRoVENT–iMIC is an international multicentre observational study in consecutive ICU patients receiving invasive mechanical ventilation during a 28–day period, expected to run in approximately 60 centres in the following Asian countries: Thailand, Vietnam, Myanmar, Pakistan, Nepal, Bangladesh, Malaysia, Sri Lanka, Maldives, Iran and India. These countries belong to the low or middle–income economies, as classified by the World Bank [22]. PRoVENT–iMIC is conducted in accordance with the declaration of Helsinki and is registered at www.clinicaltrials.gov (trial identification number NCT 03188770). Figure 1 shows the study flow–chart.

Study population

Consecutive patients intubated for ventilation during a predefined period of 28 days are enrolled. Inclusion is not restricted to patients who are intubated in the ICU, as also patients who started invasive ventilation in the emergency room, normal ward, community, or operating room directly preceding the present ICU admission are eligible for participation, without any minimum or maximum hours of ventilation needed for inclusion. The exclusion criteria include age < 18 years, use of non–invasive ventilation not followed by invasive ventilation, patients whose invasive mechanical ventilation started before the 28–day period of inclusion, and patients transferred from another hospital under invasive ventilation.

Patients will be stratified in three groups for comparison of the primary and secondary endpoints: patients without ARDS, patients without but at risk for development of ARDS, according to the Lung Injury Prediction Score (LIPS, Table 1) [23], and patients with ARDS, according to the Berlin Definition [24]. Patients with ARDS

will also be stratified according to severity of ARDS, based on the oxygenation (mild, moderate and severe ARDS categories).

Study conduct

Local investigators will screen all patients who start invasive ventilation in one of the participating ICUs during a predefined period of 28–day, lasting from 8:00 AM on the Monday of the first week to 7.59 AM on the Monday four weeks later. The exact starting date will be flexible for participating centres and shall be determined by the national study coordinator. Data collection has started in November 2017 in some sites; all sites are expected to initiate the service evaluation within one year after the overall start.

Data to be collected

Baseline and demographic variables will be collected on the day of admission, including gender, age, actual or estimated weight and height, smoking status, comorbidities including chronic obstructive pulmonary disease (COPD), active cancer, heart failure, diabetes mellitus, chronic kidney failure, liver cirrhosis and arterial hypertension, the presence of ARDS according to the Berlin Definition, the LIPS, reason for ICU admission. On the day of start of invasive ventilation we will document the reason for starting mechanical ventilation, and whether the patient received non-invasive ventilation before intubation.

Every day, until day 3 from admission in the ICU, until ICU discharge or death, whichever comes first, the ventilation status and ventilation characteristics will be collected, including ventilation mode, V_T size, respiratory rate (set and measured), peak and plateau pressure, PEEP, inspired oxygen fraction, peripheral oxygen saturation, blood gas analysis data when available (PaO_2, $PaCO_2$, arterial bicarbonate, arterial pH),

end–tidal CO_2, when available and hemodynamic parameters like heart rate and systolic blood pressure.

Every day, until day 7, ICU discharge or death, whichever comes first, the occurrence of pulmonary complications will be scored, including new requirement of invasive ventilation after initial extubation, pulmonary infections, atelectasis, pneumothorax, pleural effusions, new pulmonary infiltrates and development or worsening of ARDS.

On the day of ICU discharge (maximum 60 days after recruitment) outcome will be recorded as follows: death, discharge to ward, to medium care or high dependency unit, discharge to home for palliative care, or transfer to another ICU. The date of extubation, reintubation and tracheostomy (if performed) will also be recorded in this moment.

Study endpoints

The primary endpoint is V_T–size in millilitres per kilogram of predicted body weight (ml/kg PBW) and PEEP in centimetres of water (cm H_2O) used amongst diverse ICU patient categories during the first three days of mechanical ventilation. Secondary clinical endpoints include other ventilation parameters (including respiratory system driving pressure, the proportion of patients at risk of ARDS as stratified by the LIPS, or ARDS defined by the Berlin Definition, the occurrence of pulmonary complications, length of stay in ICU, duration of invasive ventilation and all–cause ICU–mortality.

Definitions

All cause ICU–mortality is defined as any death in the ICU. ICU length of stay is defined as the time between ICU admission and ICU discharge or death in ICU. The number of days of ventilation is defined as time between endotracheal intubation and successful

extubation (in case of intermittent mechanical ventilation via a tracheostomy, every day a patient needs ventilation counts as one extra day, irrespective of the duration of ventilation on that specific day). In case of non–invasive ventilation, the duration will be assessed separated from the assessment of invasive ventilation. The presence of spontaneous activity will be identified by any recorded difference between the set and measured respiratory rate.

Driving pressure will be calculated by subtracting the level of PEEP from the plateau pressure (Pplat in volume–control ventilation) or maximal airway pressure (Pmax in pressure–control ventilation). Pplat and Pmax are considered reliable for this calculation if the patient is receiving complete ventilatory assistance without evidence of spontaneous activity, i.e., only when the set respiratory rate equals the measured respiratory rate. Peak airways pressures will not be used to compute driving pressure as these represent a poor surrogate of the plateau pressure. Only pulmonary complications that occur after the first 24 hours of invasive ventilation will be considered in analysis, as events preceding this time point may very well be considered the potential reason for intubation. A pulmonary infection requires the presence of new or changed lung opacities on chest radiography and/or new or changed sputum plus at least a temperature > 38.3 °C or a white blood cell count >12,000 per microliter of blood. Atelectasis require the presence of increased density (lung opacity) on one or more chest radiographs with displacement of the fissures toward the area of atelectasis, crowding of pulmonary vessels and bronchi in the atelectatic region, upward displacement of hemidiaphragm ipsilateral to the side of atelectasis, that may be accompanied by shift of the mediastinum or hilum towards the affected area and compensatory overinflation in the unaffected lung [25]. Pleural effusion is suggested by

lung opacification with shift of the mediastinum, hilum or hemi–diaphragm towards the non–affected area. Pneumothorax requires the presence of air in the pleural space with no vascular bed surrounding the visceral pleura. ARDS is defined according to the Berlin Definition [24] with alternative oxygenation criteria based on SpO_2/FiO_2 applicable only when blood gas analysis data is unavailable (Table 2a and 2b) [26,27]. Worsening of ARDS is defined as any change in the prior classification (i.e., from mild to moderate or severe ARDS, or from moderate to severe ARDS).

Data management

Data will be collected from a paper medical chart, or an electronic patient data management system if available. Local investigators transcribe the collected data directly onto an anonymized internet–based electronic CRF (REDCap – Research Electronic Data Capture [28], www.projectredcap.org). In some centres data may be recorded on paper CRF and successively transcribed on the electronic CRF at a later time point. Access to the data–entry system is protected by a personalized username and password. The data will be kept on a central secured server located at the Hospital Israelita Albert Einstein, Sao Paulo, Brazil. The structure of the electronic CRF is detailed in Figure 2. A screening–log with limited patient data will be completed with all the included and excluded patients during the enrolment window. Participating centres are instructed to enter data for the daily follow–up using values obtained as close as possible to 08:00 AM, but only when the patient is stable at that time point. The study day for the recording of pulmonary complications will be defined as the natural 24h period from 00:00 until 23:59, to ensure that data is captured only once. Data for ICU–discharge will be collected until a maximum of 60 days after ICU admission, after which the CRF for that patient will be closed.

Study sites

PRoVENT–iMIC will be conducted in 11 Asian countries, with a varying number of ICUs per country. Participating ICUs are selected on the basis of willingness to participate. There are no a priori established requirements for participation, and private as well as public centres are eligible to represent real–life practices. A one–time web–based pre–study survey on structure, organizational aspects and delivery of care in the participating centres will be performed. Each participating centre is surveyed once regarding the following information: hospital characteristics (private vs. public), ICU characteristics (medical vs. surgical vs. mixed, and open vs. closed, number of ICU beds, annual number of patient admitted, number of ventilators available, and other organ support measures), and staffing (nurse to patient ratio, physician to patient ratio, presence of specialized medical staff, and overnight coverage).

Statistical Analysis Plan

No formal sample size calculation was performed, but we expect each centre to enrol 20 to 40 patients in the allocated time period, yielding a total of 1,200 to 2,400 patients. We consider this figure sufficient to analyse the study endpoints.

Normally distributed variables will be expressed by their mean and standard deviation; not normally distributed variables will be expressed by their medians and interquartile ranges; categorical variables will be expressed as n (%). In test groups of continuous normally distributed variables, Student's t-test will be used. Likewise if continuous data are not normally distributed the Mann Whitney U test will be used. Categorical variables will be compared with the Chi-square test or Fisher's exact test or when appropriate as relative risks. Statistical uncertainty will be expressed by 95% confidence levels.

The primary outcome (V_T size [ml/kg PBW] and PEEP [cm H_2O] levels during the first three days of mechanical ventilation) – will be analysed and compared between patients at no risk for ARDS, patients at risk for ARDS and in patients with ARDS (in case the diagnosis of ARDS could be made on admission). If the data is normally distributed, one way Analysis of Variance (ANOVA) or two–way ANOVA assessing the time–interaction between groups and days of observation will be used. When not normally distributed the Kruskal–Wallis test or Friedman test assessing the time–interaction between groups and days of observation will be used.

Univariate analysis will be performed to identify potential factors associated with outcomes including, but not limited to, ventilator settings (in particular V_T and PEEP). A multivariate logistic regression model will be used to determine which of those factors are independent. A stepwise approach will be used to enter new terms into the model, with a limit of $P < 0.2$ to enter the terms. Time to event variables is analysed using Cox regression and visualized by Kaplan–Meier.

Time–course variables (e.g. repeated measures of ventilator parameters, vital signs, oxygenation parameters and others) are also analysed by linear mixed model. The linear mixed models procedure expands the generalized linear model (GLM) so that the data are permitted to exhibit correlated and non–constant variability.

Pre–specified subgroups in the analyses studying potential associations between ventilator settings and outcome will be: (1) patients at low risk of ARDS vs. patients at risk of ARDS; (2) patients without ARDS vs. patients with ARDS; (3) reason for ICU admission; and (4) reason for start of invasive ventilation. Statistical analyses will be conducted using R (www.r-project.org). A *P*–value of less than 0.05 will be considered statistically significant.

Study organization

The Steering Committee is composed of a selection of PROVE Network investigators plus the national coordinators from each participating country. These investigators were involved in the design of PRoVENT–iMIC. National coordinators are responsible for identifying and recruiting local participating centres. They assist and train the local investigators and oversee the conduct of the study, including administrative management, record keeping and data management. Local investigators in individual participating centres will provide scientific and structural leadership, ensuring local ethical and regulatory approvals are obtained before start of patient inclusion. National Coordinators and Local Investigators are expected to guarantee the quality and security of the data collected.

Prior to start of the study, study teams in each centre will undergo a web–based training session on how to capture data in the electronic CRF. All study team members will be provided with a manual of operations with instructions on how to accurately fill the forms and the screening log. Incomplete or incorrectly entered electronic CRFs will be signalled to the local investigators by the national and international coordinator, for further review of the missing or flagged data.

Patient and Public Involvement

Patients and public were not directly involved in any phase of this study.

ETHICS AND DISSEMINATION

The Oxford Tropical Research Ethical Committee (OxTREC) at the University of Oxford, United Kingdom, exempted the study from ethical review on the 9th of June 2017. Data management, monitoring and reporting of the study will be performed in accordance with the International Conference on Harmonization – Good Clinical Practice guidelines.

All participating centres will also submit the study protocol to the national or local Institutional Review Board for ethical judgment, as applicable by the current regulations in the country. Due to the strict observational design and anonymous collection of data, informed consent may not be required in most countries. However, where informed consent is required, this must be approved by the local ethical committee before the start of inclusion.

The study will be reported following the Strengthening the reporting of Observational Studies in Epidemiology (STROBE) statement guidelines and checklists [29]. The results of this study will be published in a peer–reviewed medical journal. After publication of the primary results, on request the pooled dataset will be available for all members of the PRoVENT–iMIC collaboration for secondary analysis, after judgment and approval of scientific quality and validity of the proposed analysis by the Steering Committee.

DISCUSSION

PRoVENT–iMIC is designed to characterize the epidemiology, ventilator management, occurrence of pulmonary complications and outcomes in invasively ventilated patients in an estimated 60 ICUs in 11 Asian countries. The results of PRoVENT–iMIC will help to understand current ventilation practice in South and Southeast Asia, particularly with respect to variability in ventilator settings amongst patients without, at risk for or with established ARDS. Results of this study will be used to plan future trials of ventilation in ICU patients in these settings.

PRoVENT–iMIC has several strengths. First, its prospective design will allow a higher accuracy of data capturing with regard to exposures, confounders and endpoints compared to studies that used a retrospective design [30]. While a prospective design may cause sources of bias or establish causal effects, it minimizes the chance of residual confounding by unmeasured variables, a common limitation with a retrospective design, as has frequently been used in mechanical ventilation epidemiological studies [31–33]. We will have a sample size large enough to obtain precise estimates of pulmonary complications and ICU mortality and to examine potential associations between ventilation practice and patient outcomes. Second, the study sample is not restricted to certain patient diagnostic categories. Third, the attention on ventilation practice will provide robust data on this specific domain while the 7 days follow–up will allow precise recording of pulmonary complications at their origin. And finally, the wide representation of Asian countries will allow inferences on geo–economic differences in epidemiology, management and outcomes of mechanical ventilation across the entire subcontinent.

The focus on South and Southeast Asia follows our scarce knowledge about clinical practices and ventilation strategies used in critically ill patients in this and other resource–limited settings [21]. The burden of critical illness in low– and middle–income countries is higher than generally perceived and it is expected to increase with an aging population [34]. Additionally, ICUs are increasingly being set up in the region, especially in busy urban settings. A recent survey highlighted considerable variation in structure, organization and critical care delivery in Asian ICUs, but did not shed light on ventilation management and patient–centred ventilation–associated outcomes [35]. This information, however, is crucial for future trials of ventilation in ICU patients in these settings, as we need to know whether critically ill patients across Asia equally benefit from lung–protective ventilation as those in Western countries. Additionally, for proper power calculations, information with regard to potential primary endpoints, like the incidence of development of ARDS, duration of ventilation or death, is highly needed. PRoVENT–iMIC will be the first observational study that can provide this information for settings in South Asia. Results restricted to individual settings could also be valuable for local clinicians seeking to improve their local practice, training planning and identify local priorities for quality improvement within their departments.

There is now strong evidence–based support for various ICU process–based interventions such as lung protective ventilation[36], conservative fluid management strategies[37] and weaning protocols [38]. While centre– or country–specific practices or restrictions of resources are potential challenges that affect implementation of all these interventions, we focus on the management of ventilation and especially on the employment of lung–protective ventilation where feasibility may represent an issue specific to resource–limited settings. Recent literature has underlined the potential role

of the driving pressure (the pressure amplitude during each artificial breath) and its determinants in the development of ventilator–associated lung injury. Results from PRoVENT–iMIC will provide further data to enable us to discriminate the effects of V_T size, PEEP and driving pressure on outcomes in patients with, at risk of, or without ARDS.

PRoVENT–iMIC will provide important data regarding outcomes following invasive ventilation, including a wide range of clinically important pulmonary complications. Historical studies from low–resource settings documented mortality rates to exceed 70% [14–16]. However more recent data from South America and India have documented mortality rates of ~40%, similar to that in high–income countries[17,18]. This suggests that mortality in ventilated patients has the potential to improve in low–resource settings [12,13,39]. Although many factors may influence mortality, several underappreciated factors related to invasive ventilation may have contributed, including reduced need for invasive ventilation per se, improvements in safety of invasive ventilation and in liberation from invasive ventilation.

Our interest in patients at risk of ARDS follows a global recent shift in ARDS research. It is now clear that ARDS is rarely present at the time of the initial healthcare encounter, and typically develops during the hospital course, usually between days 2 and 5 in patients with predisposing conditions or risk factors [40]. Hence increasing efforts are being directed toward early identification of patients at risk with a goal of prevention and early treatment prior to the development of a fully established syndrome. This is probably equally important in resource–limited settings where the predisposing conditions and risk modifiers for ARDS may differ and limited escalation of therapy is often the case. PRoVENT–iMIC will be the first study to evaluate prospectively the role

of LIPS in these settings. Although the poor predictive accuracy of the LIPS does not currently support its use in everyday clinical practice [41], it has enabled enrolment in clinical trials of ARDS prevention [23] and may yield an initial idea on the patients at risk of and disease progression in the Asian settings under study.

PRoVENT–iMIC has some noticeable shortcomings. The definition of 'middle–income' country is rather artificial as the level of health expenditure, local resources and other geo–cultural factors might affect the processes of care in a larger extent than national income classification. Despite the inclusion of ICUs from 11 countries, which improves study generalizability, caution is needed when applying the results to supposedly similar settings, as substantial intra– and trans–national variations in ICU resources, staffing and organization exist. Second, the case report form used in PRoVENT–iMIC was designed so that it would not induce excessive work–load for the participating centres. Therefore, we decided not to collect data regarding extra–pulmonary complications and hospital–discharge outcomes, neither the amounts of sedation used and sedation levels. Similarly, due to the time window restricted to the ICU stay, we will apply the LIPS at ICU admission and not in the first 6 hours after hospital admission, as originally designed. Mortality may be underestimated in some settings where due to local practices there is the possibility to be discharged home in case of terminal conditions or family decision. To address this we made sure the data collection form captures this event whenever it represents the reason of discharge. Third, due to the limitation of laboratory data we will have a limited dataset that will not comprise daily severity scores useful for statistical controlling purposes. Also, the conceivable limitation in blood gas analysis and radiology exams may limit the documentation of insurgence or worsening of ARDS and other pulmonary complications.

Fourth, as in patients on pressure–control modes flow might not reach zero during inspiration, Pmax might overestimate alveolar pressure, hence overestimating driving pressure. An end-inspiratory occlusion could solve this problem, but is almost never performed in many centers. As this study only uses data that is collected as part of standard care, all analysis regarding driving pressure will be done separately for patients on pressure–control modes and volume–control modes. Finally, we cannot exclude that ventilator settings applied by treating physicians might be biased by the participation in the study, a problem that also existed in prior multinational studies [11,12]. Also participation in international studies like PRoVENT–iMIC always bears the risk of biased to those centres that do not fully or reliably represent ICU–care in general in the participating countries.

CONLUSIONS

PRoVENT–iMIC is designed to understand the epidemiology, practice of ventilation, and outcomes of critically–ill patients receiving invasive ventilation in a large set of South Asian countries. Results of this study could help identify practices that may best explain differences in outcomes, and could be used in designing new trials of ventilation in these settings.

Author affiliations

Contributors

LP, AGA, ASN, AMD and MJS were equally responsible for writing of the manuscript and participated in study design. FP, PP participated in study design and assisted in writing of the manuscript. AA, AB, KC, AF, RaH, ReH, MH, HAI, KI, SI, GK, BK, HM, BN, RP, SS, LT, SG, NNT, NMY, MGdA reviewed the manuscript and agreed with submission.

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Competing interests

None

Ethics approval

The Oxford Tropical Research Ethical Committee (OxTREC) at the University of Oxford, United Kingdom, exempted the study from ethical review on the 9th of June 2017. IRB approval was obtained from Sri Lanka, Bangladesh and Malaysia and is underway in Myanmar, Iran, India, Vietnam, Thailand, Nepal, Pakistan and Maldives.

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FIGURE LEGENDS

Figure 1: Flowchart of inclusion of PRoVENT–iMIC

Abbreviations: MV, Mechanical Ventilation; LIPS, Lung Injury Prediction Score; ARDS, Acute Respiratory Distress Syndrome.

Figure 2. Sequence of data submission in the electronic case report form

Abbreviations: LIPS, Lung Injury Prediction Score; MV, mechanical ventilation, ARDS, Acute Respiratory Distress Syndrome; CPE, cardiogenic pulmonary oedema; ICU, Intensive Care Unit.

Table 1. Lung Injury Prediction Score (LIPS) calculation worksheet [17,34]

Predisposing Conditions	Score	Risk Modifiers	Score
Shock	2	Alcohol Abuse	1
Aspiration	2	BMI > 30 kg/m^2	1
Sepsis	1	Hypoalbuminemia	1
Pneumonia	1.5	Chemotherapy	1
High-Risk Surgery		FiO_2 > 0.35 (> 4 l/min)	2
Orthopedic Spine	1	RR > 30 bpm	1.5
Acute Abdomen	2	SpO_2 < 95%	1
Cardiac	2.5	Acidosis (pH < 7.35)	1.5
Aortic Vascular	3.5	Diabetes Mellitus*	- 1
Emergency surgery	1.5		
High-Risk Trauma			
Traumatic Brain Injury	2		
Smoke Inhalation	2		
Near-Drowning	2		
Lung Contusion	1.5		
Multiple Fractures	1.5		

Abbreviations: BMI, body mass index; FiO_2, fraction of inspired oxygen; RR, respiratory rate; SpO_2, pulse oximetry oxygen saturation.
*(To consider only in septic patients)

Table 2a. The Berlin definition of ARDS

Criteria	Definition		
Time	Within one week of a known clinical insult, or new/worsening respiratory symptoms		
Chest imaging[1]	Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules		
Origin of oedema	Respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment to exclude hydrostatic oedema if no risk factor present (e.g., echocardiography)		
Oxygenation[2]	Mild	Moderate	Severe
	$200<PaO_2/FiO_2 \leq 300$	$100<PaO_2/FiO_2 \leq 200$	$PaO_2/FiO_2 \leq 100$
	PEEP or CPAP[3] ≥ 5 cm H_2O	PEEP ≥ 5 cm H_2O	PEEP ≥ 5 cm H_2O

Abbreviations: ARDS, acute respiratory distress syndrome; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure.
[1]chest X–ray or CT scan; [2]if altitude higher than 1,000 meters, correction factor should be made as follows: PaO_2/FiO_2 x (barometric pressure/760); [3]this may be delivered noninvasively in the mild acute respiratory distress syndrome

Table 2b. Alternative Oxygenation criteria (if PaO_2 data unavailable)

Criteria	Mild ARDS	Moderate ARDS	Severe ARDS
Oxygenation	$235<SpO_2/FiO_2 \leq 315$	$150<SpO_2/FiO_2 \leq 235$	$SpO_2/FiO_2 \leq 150$
	PEEP or CPAP≥5 cmH2O	PEEP ≥ 5 cmH2O	PEEP ≥ 5 cmH2O

Abbreviations: SpO2, pulse oximetry oxygen saturation; FiO2, fraction of inspired oxygen

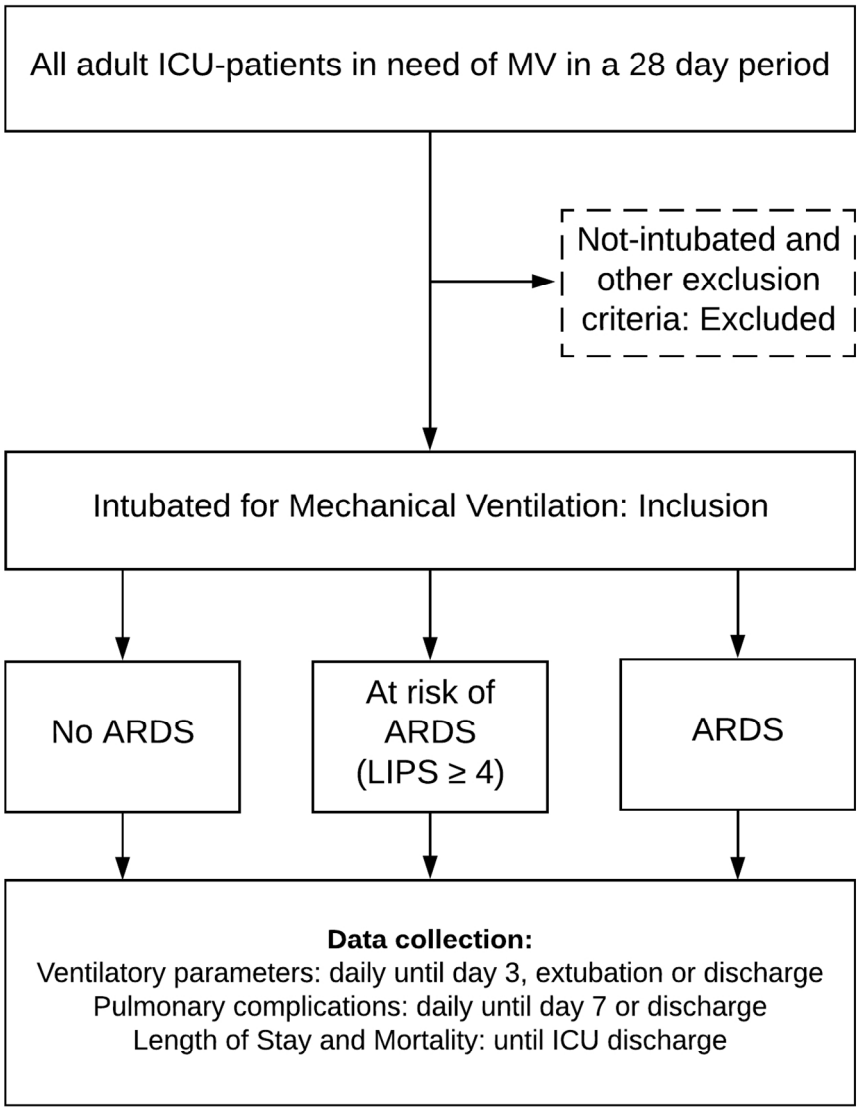

Figure 1. Flowchart of inclusion of PRoVENT–iMIC. Abbreviations: MV, Mechanical Ventilation; LIPS, Lung Injury Prediction Score; ARDS, Acute Respiratory Distress Syndrome.

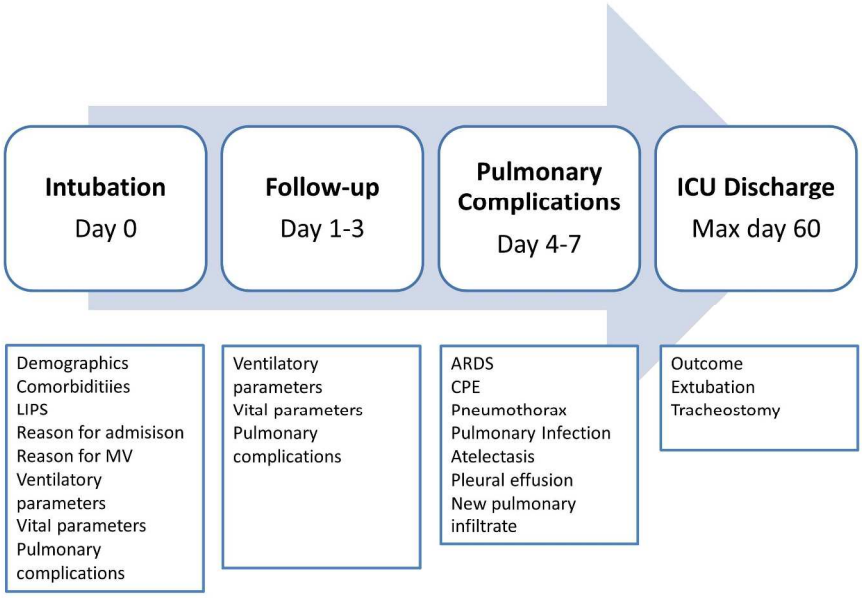

Figure 2. Sequence of data submission in the electronic case report form‼ ┼ . Abbreviations: LIPS, Lung Injury Prediction Score; MV, mechanical ventilation, ARDS, Acute Respiratory Distress Syndrome; CPE, cardiogenic pulmonary oedema; ICU, Intensive Care Unit. ‼ ┼

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