PRoVENT-IMIC: Statistical Analysis Plan

updated 20 Dic 2018

General description of statistical methods

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.

Time to ICU discharge will be analysed as a time to event variable using Cox proportional hazard models and visualized by Kaplan–Meier curves. Time–course variables (e.g. repeated measures of ventilatory parameters, vital signs, oxygenation parameters and others) will be analysed using mixed–effect longitudinal models with random intercepts for patients and centers; time will be treated as a continuous variable. Multiple imputation of missing values will be considered when appropriate. No correction for multiple comparisons are pre-specified, thus, all the findings should be viewed as exploratory. Statistical analyses will be conducted using R (www.r-project.org). A *P*–value of less than 0.05 will be considered statistically significant.

Baseline descriptive statistics

Patients baseline characteristics will be presented as shown in **dummy Table 1.** The predicted bodyweight of male patients will be calculated as 50+0.91(height [cm]-152.4) and for female patients as 45.5+0.91(height [cm]-152.4). Patients will be grouped based on the risk of ARDS defined as a Lung injury prediction score (LIPS) equal or greater than 4.

Analysis of the primary outcome

The primary outcomes (V_T size [ml/kg PBW] and PEEP [cm H_2O] levels during the first three days of mechanical ventilation), alike other ventilator settings – will be reported as in **dummy Table 2.** Variables that were collected daily (e.g. ventilator

parameters, respiratory rates, SpO2) will be presented as median [IQR]. They 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). Also, the ventilatory variables over the first three days will be presented in line plots and the *p* value will be calculated using mixed–effect longitudinal models with random intercepts for patients and centers and an interaction between time and the risk for ARDS as fixed effect; time will be treated as a continuous variable.

Scatterplots will be used to present distributions of V_T versus PEEP, V_T versus respiratory rate, V_T versus plateau pressure and V_T versus driving pressure. Cut-offs to form matrices will be based on widely accepted values for each variable, specifically 8 ml/kg PBW for V_T, 14 breaths per minute for respiratory rate, 30 cmH2O for plateau pressure, 5 cmH20 for PEEP and 15 cmH2O for driving pressure. 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).

Analysis of the secondary outcomes

The number of patients developing a pulmonary complication during the first 7 days (excluding first day of mechanical ventilation) and patient outcomes at ICU discharge will be reported in absolute numbers and percentages (**dummy Table 3**).

Univariate analysis will be performed to identify potential factors associated with ICU mortality and development of pulmonary complications including, but not limited to, ventilator settings (in particular V_T and PEEP at day 0). Relevant covariates included in the final mixed-effect multivariable model will be identified as those with $p < 0.2$ in the univariable model (including participating center as a random effect), those with clinical relevance and without statistical association with other relevant variables. The linearity of each continuous predictor with the log odds outcome will be checked graphically and, if not present, a log-transformation will be performed. Pearson correlation coefficients will be used to assess collinearity between predictors. Since a high collinearity between peak, plateau and driving pressure is expected, the main model will consider the variable with the higher amount of measurements between peak or plateau pressure. Driving pressure will be considered in a sensitivity analysis, excluding PEEP, peak and plateau pressure. Finally, the intraclass correlation coefficient (ICC) will be assessed. The ICC

represents the ratio of between-site variance to total variance, ranging from 0 to 1.

Potential associations between ventilator settings and outcome will be explored in pre–specified subgroups by building a model in each category. The subgroups are: (1) patients at low risk of ARDS versus patients at risk of ARDS; (2) patients without ARDS versus patients with ARDS; (3) reason for ICU admission and (4) reason for start of invasive ventilation.

Supplementary information

- Participant ICU structure and organizational descriptives will be reported in **supplementary dummy Table 1,** aggregated per country.

Dummy Table 1. Baseline patient characteristics

	All patients (n=)	At risk of ARDS (n=)	Not at risk of ARDS (n=)	*P* – value
Age (years)	mean ±SD or median [IQR]	mean ±SD or median [IQR]	mean ±SD or median [IQR]	
Sex				
female	n/total (%)	n/total (%)	n/total (%)	
Country				
Thailand	n/total (%)	n/total (%)	n/total (%)	
Vietnam	n/total (%)	n/total (%)	n/total (%)	
Sri Lanka	n/total (%)	n/total (%)	n/total (%)	
Maldives	n/total (%)	n/total (%)	n/total (%)	
Bangladesh	n/total (%)	n/total (%)	n/total (%)	
Pakistan	n/total (%)	n/total (%)	n/total (%)	
India	n/total (%)	n/total (%)	n/total (%)	
Malaysia	n/total (%)	n/total (%)	n/total (%)	
Myanmar	n/total (%)	n/total (%)	n/total (%)	
Iran	n/total (%)	n/total (%)	n/total (%)	
Nepal	n/total (%)	n/total (%)	n/total (%)	
Severity of illness, SOFA score				
Total	median [IQR]	median [IQR]	median [IQR]	
Pulmonary	median [IQR]	median [IQR]	median [IQR]	
Haematological	median [IQR]	median [IQR]	median [IQR]	
Liver	median [IQR]	median [IQR]	median [IQR]	
Circulation	median [IQR]	median [IQR]	median [IQR]	
Neurology	median [IQR]	median [IQR]	median [IQR]	
Renal	median [IQR]	median [IQR]	median [IQR]	
LIPS	mean ±SD or median [IQR]	mean ±SD or median [IQR]	mean ±SD or median [IQR]	
Body mass index (kg/m^2)	mean ±SD or median [IQR]	mean ±SD or median [IQR]	mean ±SD or median [IQR]	
Predicted body weigth (kg)	mean ±SD or median [IQR]	mean ±SD or median [IQR]	mean ±SD or median [IQR]	
Smoker	n/total (%)	n/total (%)	n/total (%)	
Never	n/total (%)	n/total (%)	n/total (%)	
Former	n/total (%)	n/total (%)	n/total (%)	
Current	n/total (%)	n/total (%)	n/total (%)	
Unknown	n/total (%)	n/total (%)	n/total (%)	
Reason for ICU admission				
Planned surgery	n/total (%)	n/total (%)	n/total (%)	
Emergency Surgery (excluding trauma)	n/total (%)	n/total (%)	n/total (%)	
Trauma	n/total (%)	n/total (%)	n/total (%)	
Medical condition	n/total (%)	n/total (%)	n/total (%)	
Non invasive ventilation before intubation	n/total (%)	n/total (%)	n/total (%)	
Duration (minutes)	mean ±SD or median [IQR]	mean ±SD or median [IQR]	mean ±SD or median [IQR]	
Invasive ventilation in the ward for > 12h before ICU admission	n/total (%)	n/total (%)	n/total (%)	
High risk surgery	n/total (%)	n/total (%)	n/total (%)	
Admission source				
Emergency department	n/total (%)	n/total (%)	n/total (%)	
Operating room	n/total (%)	n/total (%)	n/total (%)	
Ward	n/total (%)	n/total (%)	n/total (%)	
Directly from community	n/total (%)	n/total (%)	n/total (%)	
Reason for intubation				
Cardiac arrest	n/total (%)	n/total (%)	n/total (%)	
Anesthesia for surgery (planned)	n/total (%)	n/total (%)	n/total (%)	
Depressed level of consciousness	n/total (%)	n/total (%)	n/total (%)	
Acute respiratory failure	n/total (%)	n/total (%)	n/total (%)	
Hemodynamic instability	n/total (%)	n/total (%)	n/total (%)	
Other	n/total (%)	n/total (%)	n/total (%)	
Cause of Acute Respiratory Failure				
Community acquired pneumonia	n/total (%)	n/total (%)	n/total (%)	
Nosocomial pneumonia	n/total (%)	n/total (%)	n/total (%)	
Unplanned post operative ventilation	n/total (%)	n/total (%)	n/total (%)	
Cardiogenic pulmonary edema	n/total (%)	n/total (%)	n/total (%)	

Sepsis (other than pneumonia)	n/total (%)	n/total (%)	n/total (%)
COPD exacerbation	n/total (%)	n/total (%)	n/total (%)
ARDS	n/total (%)	n/total (%)	n/total (%)
Other	n/total (%)	n/total (%)	n/total (%)
Chronic comorbidity			
None	n/total (%)	n/total (%)	n/total (%)
Arterial hypertension	n/total (%)	n/total (%)	n/total (%)
Heart Failure	n/total (%)	n/total (%)	n/total (%)
Diabetes Mellitus	n/total (%)	n/total (%)	n/total (%)
Chronic Kidney Disease	n/total (%)	n/total (%)	n/total (%)
Liver Cirrhosis	n/total (%)	n/total (%)	n/total (%)
COPD	n/total (%)	n/total (%)	n/total (%)
Cancer	n/total (%)	n/total (%)	n/total (%)
Neuromuscular disease	n/total (%)	n/total (%)	n/total (%)
Other	n/total (%)	n/total (%)	n/total (%)

Dummy Table 2. Ventilation characteristics in first 3 days of mechanical ventilation

	Day 0			Day 01			Day 02			Day 03		
	At Risk	Not At Risk	*p* value	At Risk	Not At Risk	*p* value	At Risk	Not At Risk	*p* value	At Risk	Not At Risk	*p* value
Absolute V_T	median											
V_T (ml/kg PBW)	median											
Controlled ventilation mode	median											
Spontaneous ventilation mode	median											
$V_T \leq 7$	n/total (%)											
V_T 7–8	n/total (%)											
V_T 9–10	n/total (%)											
$V_T \geq 10$	n/total (%)											
PEEP (cm H_2O)	mean ±SD											
≤ 5	n/total (%)											
6–8	n/total (%)											
9–10	n/total (%)											
≥ 10	n/total (%)											
Mode of Ventilation												
Volume–controlled	n/total (%)											
Pressure–controlled	n/total (%)											
PSV	n/total (%)											
SIMV	n/total (%)											
APRV	n/total (%)											
Other	n/total (%)											
Peak pressure (cm H_2O)	median											
Plateau pressure (cm H_2O)	median											
Number of patients	median											
Driving pressure	median											
Static compliance (ml/cmH2O)	median											
Respiratory rate (breaths per	median											
FiO2	median											
Minute Ventilation (L/min)	median											
PaO_2/FiO_2	median											
SpO_2/FiO_2	median											
$PaCO_2$	median											
Arterial blood pH	median											
HCO_3 (mEq/L)	median											
Arterial lactate levels (meq/L)	median											
Use of neuromuscular blockers	n/total (%)											
Use of prone positioning	n/total (%)											
Use of recruitment manouvers	n/total (%)											

Dummy Table 3. Pulmonary complications observed in first 7 days of MV and clinical outcomes

Complication	All (n=)	At risk of ARDS (n=)	Not at risk (n=)
Any pulmonary complication	n/total (%)		
Pulmonary infection	n/total (%)		
confirmed by microbiology	n/total (%)		
ARDS	n/total (%)		
mild	n/total (%)		
moderate	n/total (%)		
severe	n/total (%)		
Pneumothorax	n/total (%)		
Pleural effusion	n/total (%)		
Atelectasis	n/total (%)		
Cardiogenic pulmonary edema	n/total (%)		
New pulmonary infiltrates	n/total (%)		
Outcome			
Death in ICU	n/total (%)		
Transferred to ward	n/total (%)		
Discharged home	n/total (%)		
Transferred to other ICU	n/total (%)		
Transferred to medium care or HDU	n/total (%)		
Palliative care	n/total (%)		
Duration of MV (days)	mean ±SD or median [IQR]		
Length of stay in ICU	mean ±SD or median [IQR]		
Tracheostomy	n/total (%)		

Supplementary Dummy Table 1. Participating centers characteristics, aggregated per country

Country	Country1	Country2	…Country10
Number of participating centers			
Hospital status			
Private	n/total (%)		
Public	n/total (%)		
Hospital type	n/total (%)		
Academic	n/total (%)		
Non–academic	n/total (%)		
Type of population served			
Urban	n/total (%)		
Rural	n/total (%)		
Mixed	n/total (%)		
Type of ICU			
Surgical	n/total (%)		
Medical	n/total (%)		
Cardiothoracic	n/total (%)		
Neurological	n/total (%)		
Mixed	n/total (%)		
ICU arrangement			
Open	n/total (%)		
Closed	n/total (%)		
Total number of beds in Hospital	mean ±SD or median [IQR]		
Number of beds in ICU	mean ±SD or median [IQR]		
Total number of ICU admissions in 2017	mean ±SD or median [IQR]		
Total number of ICU admissions during the PRoVENT-iMIC study period (28 days)	mean ±SD or median [IQR]		
ICUs involved in research activities	n/total (%)		
Total number of mechanical ventilators in unit	mean ±SD or median [IQR]		
Number of functioning ventilators	mean ±SD or median [IQR]		
Type of humidification mostly used			
Active humidification			
HME			
Routine use of Non Invasive Ventilation (NIV)	n/total (%)		
Availability of high flow nasal oxygen (HFNT) devices?	n/total (%)		
Dedicated physician available in ICU 24/7	n/total (%)		
Number of staff physicians per shift	median [IQR]		

Country	Country1	Country2	…Country10
Number of doctors in training or residents per shift	median [IQR]		
Number of Nurses per shift	median [IQR]		
Usual nurse to bed ratio			
1 nurse to 1 bed	n/total (%)		
1 nurse to 2 beds	n/total (%)		
1 nurse to 3 beds	n/total (%)		
1 nurse to 4 beds	n/total (%)		
Other	n/total (%)		
Availability of renal replacement therapy	n/total (%)		
Availability of pulse oximetry for all patients	n/total (%)		
Availability of end tidal CO_2	n/total (%)		
Availability of chest x-ray apparatus			
Not available	n/total (%)		
Dedicated ICU portable apparatus	n/total (%)		
Hospital apparatus	n/total (%)		
External provider	n/total (%)		
Availability of computed tomography imaging			
Not available	n/total (%)		
In hospital	n/total (%)		
Outsourced	n/total (%)		
Availability of ultrasound apparatus			
Not available	n/total (%)		
Yes, dedicated ICU ultrasound apparatus	n/total (%)		
Yes, in hospital	n/total (%)		
Availability of blood gas analyzer in ICU	n/total (%)		