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EPIDEMIOLOGY, PRACTICE OF VENTILATION AND OUTCOME FOR PATIENTS AT RISK OF ARDS IN INTENSIVE CARE UNITS IN 16 COUNTRIES

PRACTICE OF VENTILATION IN PATIENTS WITHOUT ARDS

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*PRoVENT: PRactice of VENTilation in in critically ill patients without ARDS at onset of ventilation study (https://sites.google.com/site/proventtrial/home)
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The PRoVENT Steering Committee members & Writing Committee members are listed below; Collaborators are listed in the Supplementary Appendix (pp. 2–8)

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Contributions

The members of the PRoVENT Steering Committee designed and overviewed conduct of the study. PRoVENT collaborators, consisting of National – and Local Investigators, collected the data. The study report was written by the PRoVENT Writing Committee and revised by the PRoVENT Steering Committee. ASN and MJS had complete access to all study data and performed the analyses, with support from MGdA, and PP. ASN, MGdA, PP and MJS made the final decision to submit the report for publication. ASN was the study coordinator. ASN, MGdA, PP and MJS contributed equally to the study.

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ABSTRACT

BACKGROUND: Limited information exists about the epidemiology and outcome of intensive care unit (ICU) patients at risk of the acute respiratory distress syndrome (ARDS), and how ventilation is managed in these patients. The aim of this study is to determine the epidemiology for patients at risk of ARDS, describe ventilation management, and outcomes compared to patients at no risk.

METHODS: PRoVENT was an international multicentre prospective study of mechanically ventilated patients during one week in a sample of 119 ICUs from 16 countries in 2014–2015. The Lung Injury Prediction Score (LIPS) was used for risk of ARDS stratification. The primary outcome was the incidence of patients at risk of ARDS. Secondary outcomes included ventilatory management, development of pulmonary complications, and clinical outcomes.

FINDINGS: 935 patients fulfilled the inclusion criteria. The prevalence of patients at risk of ARDS was 30·2% (95% confidence interval, 27·2%–33·1%), and represented 0·14 cases/ICU bed over one week. Tidal volume size (V_T) was 7·9 (6·8–9·1) ml/kg PBW, similar between patients at and at no risk of ARDS. The level of positive end–expiratory pressure (PEEP) was higher in patients at risk of ARDS, though differences were minimal. Patients at risk of ARDS more frequently developed ARDS (7·7% vs. 3·2%; p = 0.004), and had higher in–hospital mortality rates. V_T was not different between patients who did and did not develop ARDS

INTERPRETATION: The prevalence of patients at risk of ARDS is high. A large proportion of patients receive high tidal volumes. Pulmonary complications occur frequently in patients at risk of ARDS, with an associated worse clinical outcome.

FUNDING: None

KEYWORDS: Acute respiratory distress syndrome; mechanical ventilation; ventilator–induced lung injury; tidal volume; positive end–expiratory pressure

INTRODUCTION

Invasive mechanical ventilation is a frequently applied intervention in intensive care unit (ICU) patients.[1,2] While ventilation usually is seen as a life–saving strategy it has a strong potential to worsen pre–existing lung injury.[3] Ventilation strategies aiming at preventing lung overdistention through the use of low tidal volumes (V_T) (≤ 6 ml/kg predicted body weight [PBW]) was found to improve outcome of ICU patients with the acute respiratory distress syndrome (ARDS).[4,5] Consequently, low V_T is seen as the key element of so–called lung–protective ventilation in patients with this life–threatening complication of critical illness. Ventilation strategies aiming at avoiding repetitive opening and closing of atelectatic lung tissue through the use of high levels of PEEP (> 10 cm H_2O) was found beneficial in patients with moderate or severe ARDS only in an individual patient data meta-analysis of three randomized controlled trials.[6] Consequently, several guidelines suggest to use higher than lower levels of PEEP in patients with moderate to severe ARDS.[7,8]

There is growing evidence that ventilation can not only worsen but also induce lung injury, especially in patients at risk of ARDS.[3,9] Moreover, meta–analyses of observational studies and randomized controlled trials suggest improved outcomes with the use of low V_T during ventilation in ICU patients who did not have ARDS at start of ventilation.[10-13] Convincing evidence, however, remains lacking.[14] Association between ventilation at low V_T and increased needs for sedation and prolonged use of muscle paralysis are some of the reasons for why clinicians remain reluctant to use low V_T in patients without ARDS.[14] Whether PEEP benefits patients without ARDS is even more uncertain.[9,15-17] The risk of overdistension, potentially inducing additional lung injury, with higher levels of PEEP have made clinicians reluctant to use PEEP as liberal in patients with uninjured lungs as in patients with ARDS.[18,19]

Preventing ARDS may be more effective strategy than treating ARDS in improving outcomes of critically ill patients. One major obstacle to preventive studies is the inability to anticipate which patients are likely to develop ARDS.[20] Epidemiologic data suggest that the syndrome is rarely present at hospital admission, but develops over a period of hours to days in a subset of patients at risk of ARDS,[20] with considerable impact on outcome. While it is in particular this group of patients in which lung–protection has a potential to improve outcome, it is unknown how ventilation is currently managed in these patients, and whether it differs from that in patients at low risk of ARDS.

We undertook the 'PRactice of VENTilation in critically ill patients without ARDS at onset of ventilation study' (PRoVENT) to 1) determine the epidemiology and outcomes of patients at risk of ARDS, 2) to describe and compare ventilation management in patients at risk versus patients at no risk of ARDS, and 3) to determine if ventilation at higher V_T is associated with higher incidence of ARDS.

METHODS

Study design and study sites

PRoVENT was an investigator–initiated international multicentre observational cohort study. Part of the study protocol was published previously (and is available in the Supplementary Appendix).[21] The members of the Writing Committee of PRoVENT designed the study, drafted the analysis plan, analysed the data, prepared the final report and took the decision to submit the manuscript after review by the members of the Steering Committee of the study. PRoVENT was registered at Clinicaltrials.gov (NCT01868321).

Study sites were recruited through direct contact among members of the Steering Committee and potential National Coordinators. Approved National Coordinators contacted Local Coordinators, who sought approval from their respective Institutional Review Boards (or Research Ethics Committees), and if required obtained written informed consent from individual patients. National Coordinators assisted Local Coordinators and monitored the study according to the 'International Conference on Harmonization (Good Clinical Practice)' guidelines. Local Coordinators ensured integrity and timely completion of data collection.

Study population

Consecutive patients under invasive ventilation were eligible for participation if admitted in a predefined period of one week, as selected by the National Coordinator for each country, but within the time frame ranging from January 2014 to January 2015. Inclusion criteria were: 1) age ≥ 18 years; and 2) admission under ventilation, which could have been initiated outside the hospital, in the emergency room, in the normal ward, or in the operating room, *or* 3) start of ventilation in the ICU, after admission. Patients in whom ventilation was started before the study recruitment week of PRoVENT, patients receiving only non–invasive ventilation or transferred from another hospital under mechanical ventilation were excluded. Data from

patients who fulfilled the Berlin definition for ARDS at start of ventilation[8] were collected but not included in the primary analysis.

Data collection

Baseline and demographic variables were collected on the day of ICU admission to calculate disease severity scores and the Lung Injury Prediction Score (LIPS).[20] Day 0 was defined as the first calendar day that patients received invasive ventilation, irrespective of ICU admission date. Reasons for ventilation were recorded. Every day, until ICU discharge or death, patients were evaluated for ventilation and intubation status (including tracheostomy). A 'ventilation day' was counted as any day that the patient received mechanical ventilation, irrespective of duration of mechanical ventilation during that day, and irrespective whether this was done through an orotracheal tube or tracheostomy.

The case report form (available in the Supplementary Appendix) automatically prompted investigators to provide an expanded data set until day 7, or at ICU discharge or ICU death. Ventilator settings and parameters, vital signs, transfusion requirements, daily fluid balances, sedation scores, and Sequential Organ Failure Assessment (SOFA) scores were recorded every day, close to 08:00 AM until end of mechanical ventilation, ICU discharge or death, as appropriate. Rescue therapies for refractory hypoxemia, including recruitment manoeuvres, inhaled nitric oxide, extracorporeal membrane oxygenation (ECMO) or extracorporeal removal of carbon dioxide ($ECCO_2R$), high frequency oscillatory ventilation (HFOV) and prone positioning, were recorded. The risk of death was derived from APACHE II or SAPS III.

Patient data were anonymized before entry onto a password secured, web–based electronic case record form (Oracle Clinical, Redwood Shores, CA, USA). In addition, prior to analysis, all data were screened for potentially erroneous data and outliers. These data were verified or corrected by site investigators. We followed the Strengthening the Reporting of

Observational Studies in Epidemiology (STROBE) statement guidelines for observational cohort studies.[22]

Study outcomes

The primary outcome was the ICU incidence of patients at risk of ARDS. Secondary outcomes included ventilation management, the occurrence of ARDS according to Berlin definition,[8] and other pulmonary complications like pneumonia, pneumothorax, pleural effusion, atelectasis, and cardiogenic pulmonary oedema (the definition of each complication is explained in the Protocol and in eTable 1). Pulmonary complications, including ARDS, were diagnosed using chest radiographs and laboratory parameters by local investigators in each site. We provided complete definitions of the pulmonary complication of interest to increase efficiency and accuracy of pulmonary diagnoses.

Other endpoints included duration of ventilation expressed in the number of ventilator–free days and alive at day 28 (calculated as the number of days from weaning from invasive ventilation to day 28; patients who died before weaning were considered to have zero ventilator–free days); ICU and hospital length of stay; and ICU–, hospital– and 90–day mortality.

Analysis plan and statistical analyses

Part of the analysis plan was published before.[21] Patients were stratified to risk or no risk of ARDS group based on the LIPS (LIPS ≥ 4 *vs.* < 4, respectively). Ventilation settings are presented for all patients and focused on the first day only. No adjustment for multiplicity was applied across the analyses. Therefore, the results do not claim confirmatory statistical evidence. The evidence level of the results, however, is more than exploratory, due to the pre-specification of analyses in the protocol. Nevertheless, for the analyses of outcomes we controlled the false discovery rate using the Benjamini-Hochberg procedure using a false discovery rate of 0·2.

The prevalence of patients at risk of ARDS was calculated by dividing the number of patients at risk of ARDS by the total number of patients without ARDS submitted to mechanical ventilation. The number of patients at risk of ARDS per ICU bed over the study period was calculated as number of patients at risk of ARDS divided by the number of ICU beds available.

Distributions of combinations of V_T size and PEEP, V_T size and respiratory rate, and V_T size and plateau pressure are presented in scatterplots. A cut–off of 8 ml/kg PBW for V_T, 14 bpm for respiratory rate, 30 cm H_2O for plateau pressure, and 5 cm H_2O for PEEP were chosen to form the matrices. These cut–offs were based on widely accepted values of each variable, or according to normal daily practice.

V_T size and PEEP level were analysed according to the following outcome subgroups: 1) development of ARDS (yes *vs.* no); 2) development of other pulmonary complications (yes versus no); and 3) hospital mortality (yes *vs.* no). Since V_T sizes in patients at risk and at no risk of ARDS, and in patients who developed ARDS and who did not develop ARDS was not different, we deviated from the original study protocol: we did not perform association analyses of the relationship between V_T size and the occurrence of ARDS.

Post–hoc analyses

In one post–hoc analysis, the ventilation parameters in patients who did not have ARDS were compared to those who fulfilled the Berlin definition for ARDS at start of ventilation, of whom also data had been collected. In a second post–hoc analysis, the driving pressure, defined as plateau pressure *minus* PEEP, was analysed following the same analysis plan as for the other ventilatory parameters. V_T and driving pressure combinations were plotted in one extra scatterplot, in which a cut–off of 15 cm H_2O for the driving pressure was used to build the matrix.

Finally, in a third post–hoc analyses we determined the accuracy of the LIPS for predicting development of ARDS using different cut–offs. For this we determined the area under the receiver operating characteristic curve (AUC-ROC), and calculated corresponding positive and negative predictive values, positive and negative likelihood ratios, and their 95% CIs. A sensitivity analysis was performed to determine the model performance at different cut-off points.

Statistical analysis

Daily–collected variables, including V_T size, PEEP level, peak and plateau pressure level *or* maximum airway pressure level (where available), respiratory rate, oxygen fraction of inspired air (FiO_2), and calculated variables including driving pressure levels and compliance, were presented as medians with their interquartile ranges. V_T size was presented as an absolute volume (ml) and volume normalized for PBW (ml/kg PBW). The PBW of male patients was calculated as equal to 50 + 0·91(centimetres of height – 152·4); that of female patients was calculated as equal to 45·5 + 0·91(centimetres of height – 152·4).[8] The amount of missing data was low; therefore no assumptions were made for missing data.

Proportions were compared using χ^2 or Fisher exact tests and continuous variables were compared using the *t* test or Wilcoxon rank sum test, as appropriate. A Kaplan–Meier estimate of the cumulative probability of unassisted breathing and survival was performed. Patients discharged from the hospital before the end of follow–up were assumed alive and without complications at this time point. We used log–rank tests to compare survival distributions in patients at and at no risk of ARDS.

To assess the impact of baseline imbalances and the association between risk of ARDS and outcomes, a frailty model was developed using centres as cluster variable. First we selected variables that sowed imbalance at baseline and included them in an univariable

model. Those variables with $p < 0{\cdot}2$ in unadjusted analysis were included in the final multivariable model.

Statistical significance was considered to be at 2–sided $p < 0{\cdot}05$. All analyses were performed with SPSS v.20 (IBM SPSS Statistics for Windows, Version 20·0. Armonk, NY: IBM Corp.), and R v.2·12·0 (http://www.R-project.org/).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Participating centres and patients

One hundred and eighty three centres from 20 countries in four continents expressed interest in participating in PRoVENT. Finally, 119 ICUs from 16 countries in four continents collected data (Figure 1). The list of participating centres, countries and respective numbers of included patients is presented in online Supplement (eTables 2 and 3). Of 1,021 patients in whom data collection had started, 86 had ARDS at start of ventilation (Figure 1). Demographics and characteristics of patients are shown in Table 1 and eTable 4.

ICU incidence of patients at high risk for ARDS

Patient at risk of ARDS represented 30·2% (95% confidence interval [CI], 27·2%–33·1%) of all ventilated patients without ARDS. There was considerable geographic variation, with Europe having 28·7% (95% CI, 25·5–31·8%) of patients at high risk of ARDS; North America, 18·2% (95% CI, 9·0–45·4%); South America, 43·4% (95% CI, 33·9–53·0%); and Oceania 27·3% (95% CI, 11·2–43·3%) (p = 0.015). Patients at risk of ARDS represent 0·14 cases/ICU bed over one week.

Ventilatory management

V_T size was typically 500 (440–580) ml, or 7·9 (6·8–9·1) ml/kg PBW, with no differences between the risk groups (Table 2). V_T size was > 8·0 ml/kg PBW in almost 30% of the patients in both risk groups (Table 2, Figure 2A). V_T was not different between patients who did and did not develop ARDS (Table 3) or other pulmonary complications (data not shown), and not different between non–survivors and survivors (data not shown). Patients at risk of ARDS received higher levels of PEEP, but the difference with patients at no risk of ARDS was minimal (6·0 [5·0–8·0] *vs.* 5·0 [5·0–7·0] cm H_2O; $p < 0·001$) (Table 2, Figure 2B). The PEEP level was higher in non–survivors, but there were no differences between patients who did and did not develop ARDS (Table 3) or other pulmonary complications (data not shown).

Pressure–controlled and synchronized intermittent mandatory ventilation were the most frequently used modes of invasive ventilation, with no differences between the two risk groups (Table 2). Furthermore, patients at risk of ARDS were ventilated at higher respiratory rates, received higher FiO_2, and had higher peak and plateau pressure levels then patients at no risk of ARDS (Table 2, Figure 2C). The driving pressure was typically 10·0 (6·0 – 13·0) cm H_2O and slightly higher in patients at risk of ARDS than in patients at no risk of ARDS (10·0 [6·7–14·0] *vs.* 9·0 [6·0–12·0] cm H_2O; $p = 0{\cdot}048$) (Table 2, Figure 2D). Descriptions of ventilatory parameters over time are shown in eFigure 1. Only the PEEP levels differed between patients at risk and at no risk of ARDS during the seven days of follow up.

Distributions of combinations of ventilation parameters are presented in Figure 3. Patients were mainly ventilated with PEEP levels ≤ 5 cm H_2O, independently from the risk of ARDS (Figure 3A). Half of the patients received ventilation with V_T of > 8 mL/kg of PBW *and* a plateau pressure < 30 cm H_2O (Figure 3B), with no differences between the two risk of ARDS groups. A combination of low V_T and a high respiratory rate was commonly observed, both in patients at and at no risk of ARDS (Figure 3C).

The use of adjunctive treatments was low but higher in patients at risk of ARDS (eTable 5). Recruitment manoeuvres were the most frequently used adjuncts. All adjunctive treatments were applied after the initial diagnosis of ARDS.

Clinical outcomes

Pulmonary complications, ARDS and pneumonia developed more frequently in patients at risk of ARDS (Table 4). The majority of patients who developed ARDS did so after the second day of ventilation (eFigure 2). There was a decreased likelihood of unassisted breathing and 90–day survival in patients at risk of ARDS (Figure 4). The number of ventilator–free days was lower (24·0 [0·0–27·0] vs. 25·0 [21·0–27·0] days; $p = 0{\cdot}002$), and the length of ICU and hospital stay, was higher in patients at risk of ARDS (Table 4). ICU,

hospital and 90–day survival were lower in patients at risk for ARDS (Table 4). The results from the false discovery rate adjustments are shown in eTable 6. There are no differences after this adjustment.

Post–hoc analyses

Of 1,021 patients, 86 patients were recognized as having ARDS at start of ventilation. V_T size was not different between patients with ARDS and patients at and at no risk of ARDS (eTable 7, eFigure 3A). Patients with ARDS, however, were ventilated with higher levels of PEEP (eTable 7, eFigure 3B).

Driving pressure was not different between patients at and at no risk of ARDS, but always lowers than in patients who started ventilation while having ARDS (eFigure 3C). Most of the patients who started ventilation while not suffering form ARDS received ventilation with low driving pressure, not different between patient at and at no risk for ARDS (Figure 3D). There was a direct relationship between driving pressure tertile and mortality rate (eFigure 4).

The LIPS had an AUC–ROC of 0.621 (95% CI, 0.528 – 0.713; p = 0.014) (eFigure 5). Specificity increased, though at a sharp decrease of the sensitivity when using higher cut–offs (eTable 8). At a cut-off of 4 the positive and negative likelihood ratios (95% CI) for development of ARDS were 1.8 (1.4 – 2.3) and 0.5 (0.3 – 0.8), respectively, with a sensitivity of 0.67 (0.49 – 0.81) and specificity of 0.63 (0.59 – 0.66). eTable 8 describes the performance of the LIPS model at different cut-off points in a sensitivity analysis.

DISCUSSION

This prospective observational study performed in 119 hospitals across 16 countries shows that a considerable proportion of patients undergoing invasive ventilation are at risk of ARDS. Approximately half of patients without ARDS receive a V_T > 8 ml/kg PBW, not different between patients at and at no risk of ARDS, and remarkably similar to patients with ARDS at onset of ventilation. PEEP levels are slightly higher in patients at risk of ARDS, but lower than in patients with ARDS at onset of ventilation. Pulmonary complications are common in patients at risk of ARDS, with associated worse outcomes.

PRoVENT is the most recent prospective study focusing on practice of ventilation in patients without ARDS at start of ventilation, and the first that shows the epidemiology for patients at risk of ARDS. It extends our knowledge of ventilation, as it compared ventilation practice in patients at risk for ARDS versus patients at no risk of ARDS. In addition, PRoVENT presents the proportions of patients who develop pulmonary complications in patients at and at no risk of ARDS, and the clinical outcomes in these two groups. The international character of PRoVENT makes its results representative for many countries. The prospective design of PRoVENT assured completeness of the data collection, and the short time frame within which data were collected avoided effect of practice changes over time. As such, the data presented here could function as a basis for new hypotheses as well as sample size calculations for future trials of mechanical ventilation. Finally, it also allows for better interpretation of previous studies and their control groups.

In the present study we found considerable geographic variation in the number of patients at risk of ARDS, ranging from 18·2% to 43·4%. It is uncertain whether this difference is a reflection of seasonal differences in the incidence of risk of ARDS, or whether it is a true difference independent from e.g., risk factors for ARDS such as influenza. It is

more likely that this difference is explained by differences in case–mixes caused by factors such as admission policies or availability of ICU beds.

The results of PRoVENT confirm those from previous investigations, reporting V_T sizes from as low as 7 to as high as 10 ml/kg PBW, but with decreasing trends over recent years.[1,8,23-31] The V_T findings suggest that there is little or no titration on the basis of the predicted body weight. Indeed, the median V_T size was typically 500 ml, with a large variance when expressed in ml/kg PBW, suggesting a lack of individualisation. Even though V_T size was lower than previously reported in ICU patients,[1,8,23-31] the observed V_T sizes could still be considered as 'too large' in many patients, as more than half of patients received V_T > 8 ml/kg PBW. Interestingly, V_T size was similar in patients at risk of ARDS and patients at no risk of ARDS, and also strikingly similar as V_T size in patients with ARDS.

The PEEP level was comparable between the two risk groups of ARDS, with 45·8% receiving PEEP > 5 cm H_2O, and only 4·9% receiving PEEP > 10 cm H_2O. The impact of use of PEEP in patients without ARDS is a matter of debate. Randomized controlled trials up till now have been too small, and mainly assessed outcomes that could suffer from bias.[15,16,32] Notably, the most recent randomized controlled trial of PEEP suggested that a higher PEEP level (8 cm H_2O compared to 0 cm H_2O) prevents pneumonia, but this trial was underpowered for this endpoint.[15]

The majority of patients received ventilation at low plateau pressures and high respiratory rates. The finding of a low plateau pressure is expected in a population of patients without uninjured lungs, in whom the respiratory system compliance is high, thus, resulting in low airway pressures, independently from the V_T size. The finding that patients received mainly low tidal volume and high respiratory rate is important, since recent evidences suggests that the use of low V_T could benefit even patients without ARDS.[2,9-14,33]

Several investigations showed an association between high driving pressure and mortality in patients with ARDS.[34,35] One recent investigation in patients undergoing intraoperative ventilation under general anaesthesia even showed an association between driving pressure and development of postoperative pulmonary complications.[36] The present study found no differences in the driving pressure between patients at *vs.* at no risk of ARDS, but shows that a higher driving pressure is associated with a higher probability of death.

Pulmonary complications are known to have important impact on outcome in surgical patients.[17] The impact of development of pulmonary complications on outcome in ICU patients without ARDS is less well understood. This study suggests that development of pulmonary complications is associated with worse outcome. The proportion of patients at risk of ARDS who finally met the definition of ARDS during follow up in the present study is similar to the proportion found in another study in patients without ARDS at onset of ventilation using the same cut–off of the LIPS.[37] Even though the specificity of the LIPS rose with higher cut–offs, we remained with a cut–off of 4, as the sensitivity became very low with each increase of the cut–off, and because this cut–off was used in the original reports on this score.[20,37] Thus, one salient finding of this study is that the LIPS may not be the best score to stratify patients without ARDS at onset of ventilation. Further refinements in prediction of ARDS are highly needed. Also, the absence of strict criteria for the diagnosis of pneumonia may lead to an incorrect diagnosis. ARDS might have been incorrectly diagnosed as pneumonia in many cases, underestimating its true incidence. Indeed, it is difficult to diagnose pneumonia in the presence of ARDS, with a cited sensitivity using conventional clinical criteria of under 50%.[38]

Simultaneously to the PRoVENT study, a multicentre prospective observational, 4–week inception cohort study called the ‘Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE’ (LUNG SAFE) was conducted.[39] Different from

the PRoVENT study, LUNG SAFE prospectively assessed the burden of, management and therapeutic approaches to, and outcomes in mechanically ventilated patients *with* ARDS, and only during the winter months in the northern and southern hemispheres. PRoVENT and LUNG SAFE together provide a unique insight in worldwide practice of ventilation in ICU patients without and with ARDS, respectively. It is worth noting that a fast majority of mechanically ventilated patients in the ICU do not have ARDS.[14]

PRoVENT has limitations that need to be addressed. First, willingness of participating centres to join the study may have caused a selection bias towards inclusion of centres with an interest in protective ventilation. Second, any prospective observational study can interfere with daily practice, since physicians could have been keener to use lung–protective ventilation settings. Third, the number of centres per country was not limited, which could have caused an overrepresentation of some countries. Similar to other epidemiological studies, access to the source data for the patients in the enrolling ICUs was restricted, and it could not be controlled whether all patients under mechanical ventilation in participating centres were enrolled.

CONCLUSION

In 119 ICUs in 16 countries the prevalence of risk for ARDS was 30·2% in patients receiving invasive ventilation. A large proportion of patients at risk of ARDS at onset of ventilation received V_T > 8 ml/kg PBW, similar to patients at no risk of ARDS. The applied PEEP level was low, and only slightly higher in patients at risk of ARDS. Patients at risk of ARDS more frequently developed pulmonary complications, including ARDS, and had worse clinical outcomes. The findings of this study suggest the potential for improvement in the management of patients without ARDS. This study also suggests that further refinements in prediction of ARDS are highly needed.

RESEARCH IN CONTEXT

Evidence before this study

There is growing evidence that ventilation may not only worsen but also induce lung injury, especially in patients at risk of ARDS. Preventing ARDS may be more effective strategy than treating ARDS in improving outcomes of critically ill patients. One major obstacle to preventive studies is the inability to anticipate which patients are likely to develop ARDS. Epidemiologic data suggest that the syndrome is rarely present at hospital admission, but develops over a period of hours to days in a subset of patients at risk of ARDS, with considerable impact on outcome. Before initiating this study, we searched the scientific literature with the terms ("mechanical ventilation") AND ("ARDS" OR "acute respiratory distress syndrome") AND ("high risk" OR "LIPS"), without any date or language restrictions. We excluded studies of patients not receiving mechanical ventilation and paediatric populations. We did not find any specific study assessing mechanical ventilation and outcomes in patients according to the risk of ARDS based on LIPS. One study using the database from the original LIPS suggested that clinicians seem to respond to ARDS with lower size of the initial tidal volume (V_T). Initial V_T, however, was not associated with the development of post–intubation ARDS or other outcomes. Nevertheless, this study neither assessed the incidence of patients at risk of ARDS nor evaluated the possible differences in the mechanical ventilation between this group of patients and those at no risk of ARDS. The aim of our study was to establish the incidence of patients at risk of ARDS in a large international cohort of mechanically ventilated patients without ARDS, and to describe and compare ventilation management in patients at risk versus patients at no risk of ARDS.

Added value of this study

This is the first multicentre, international study focusing specifically on the incidence of patients at risk of ARDS, its ventilatory management and clinical outcomes, including

pulmonary complications and mortality. It will add value to the existing evidence because of its prospective design, the consecutive collection of data from patients, the inclusion of several ICUs from different countries and continents, increasing its generalizability, and the detailed description of the ventilatory parameters, pulmonary complications and clinical outcomes.

Implications of all the available evidence

The future implication for daily clinical practice is that the incidence of patients at risk of ARDS is high and their outcomes are worse compared to patients at no risk. Early implementation of protective ventilation and other strategies in this group of patients could be associated with better outcomes. Also, the results of PRoVENT nicely add to our current knowledge of epidemiology and outcomes of ARDS patients, as described in the recently published LUNG SAFE study. Actually, the results of PRoVENT could be very useful in planning future studies, and understanding the findings of earlier studies in mechanical ventilation in ICU patients. Notably, a fast majority of ventilated ICU patients does not suffer from ARDS; but as PRoVENT shows, a considerable number of patients are at risk of this life–threatening complication. Finally, the results of PRoVENT suggest that further refinements in prediction of ARDS are highly needed.

LEGEND TO FIGURES

Figure 1 – Flow of Patient Screening and Enrolment

Abbreviations: IRB: Institutional Review Board; ARDS: acute respiratory distress syndrome; LIPS: Lung Injury Prediction Score.

Figure 2 – Ventilation parameters in patients at *vs.* patients at no risk of ARDS

Cumulative frequency distribution of tidal volume (A); cumulative frequency distribution of positive end–expiratory pressure (B); cumulative distribution of plateau pressure (C); and cumulative distribution of driving pressure (D).

Abbreviations: PEEP: positive end–expiratory pressure; PBW: predicted body weight; V_T: tidal volume

Figure 3 – Distributions of ventilatory pattern in the first day of ventilation in patients at *vs.* patients at no risk of ARDS

Distribution of tidal volume against PEEP (A); tidal volume against plateau pressure (B); distribution of tidal volume against respiratory rate (C); and distribution of tidal volume against driving pressure (D).

Abbreviations: PEEP: positive end–expiratory pressure; PBW: predicted body weight; V_T: tidal volume

Figure 4 – Outcome of in patients at *vs.* patients at no risk of ARDS

Probability of discontinuing mechanical ventilation (A); and probability of 90–day survival (B). *p values for log-rank test (unadjusted) and for the frailty model (adjusted by baseline imbalance)*

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AUTHORS' CONTRIBUTIONS

ASN designed the study, conducted the data collection, data analysis, and data interpretation, and wrote the manuscript.

CSVB designed the study, conducted the data interpretation, and reviewed the manuscript.

FDS designed the study, conducted the data collection, data interpretation, and reviewed the manuscript.

AAR designed the study, conducted the data collection, data interpretation, and reviewed the manuscript.

JC designed the study, conducted the data collection, data interpretation, and reviewed the manuscript.

RMD designed the study, conducted the data collection, data interpretation, and reviewed the manuscript.

JA designed the study, conducted the data collection, data interpretation, and reviewed the manuscript.

GH designed the study, conducted the data interpretation, and reviewed the manuscript.

SNTH designed the study, conducted the data interpretation, and reviewed the manuscript.

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MWH designed the study, conducted the data interpretation, and reviewed the manuscript.

SJ designed the study, conducted the data interpretation, and reviewed the manuscript.

IML designed the study, conducted the data collection, data interpretation, and reviewed the manuscript.

GHM designed the study, conducted the data collection, data interpretation, and reviewed the manuscript.

RMP designed the study, conducted the data interpretation, and reviewed the manuscript.

CP designed the study, conducted the data interpretation, and reviewed the manuscript.

WS designed the study, conducted the data collection, data interpretation, and reviewed the manuscript.

PS designed the study, conducted the data collection, data interpretation, and reviewed the manuscript.

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MGA designed the study, conducted the data interpretation, and reviewed the manuscript.

PP designed the study, conducted the data interpretation and reviewed the manuscript.

MJS designed the study, conducted the data analysis and data interpretation, and reviewed the manuscript.

All authors contributed to critical review and revision of the manuscript. All authors have seen and approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors declared no conflicts of interest.

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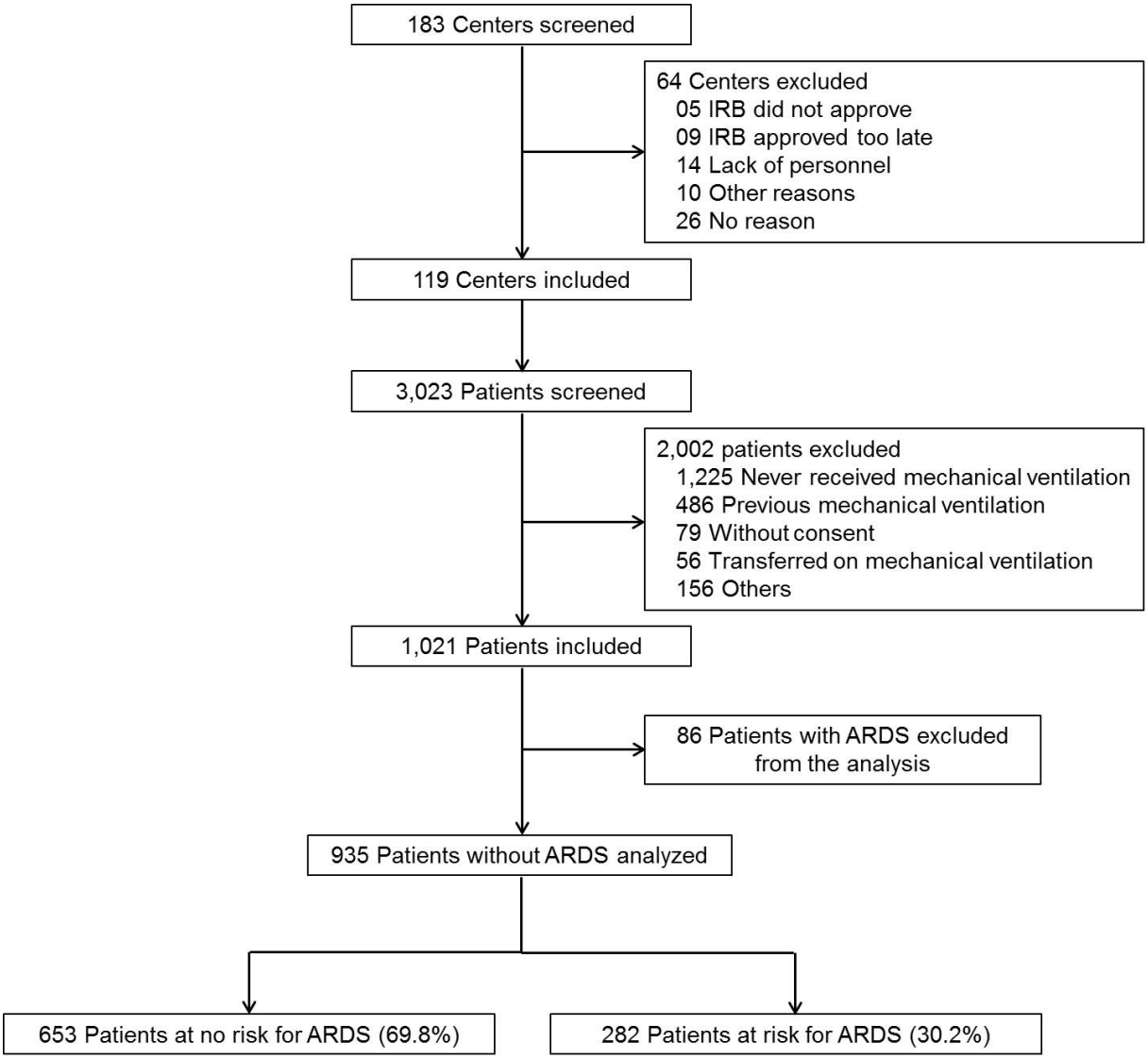
183 Centers screened
64 Centers excluded
05 IRB did not approve
09 IRB approved too late
14 Lack of personnel
10 Other reasons
26 No reason
119 Centers included
3,023 Patients screened
2,002 patients excluded
1,225 Never received mechanical ventilation
486 Previous mechanical ventilation
79 Without consent
56 Transferred on mechanical ventilation
156 Others
1,021 Patients included
86 Patients with ARDS excluded from the analysis
935 Patients without ARDS analyzed
653 Patients at no risk for ARDS (69.8%)
282 Patients at risk for ARDS (30.2%)

FIGURE 1

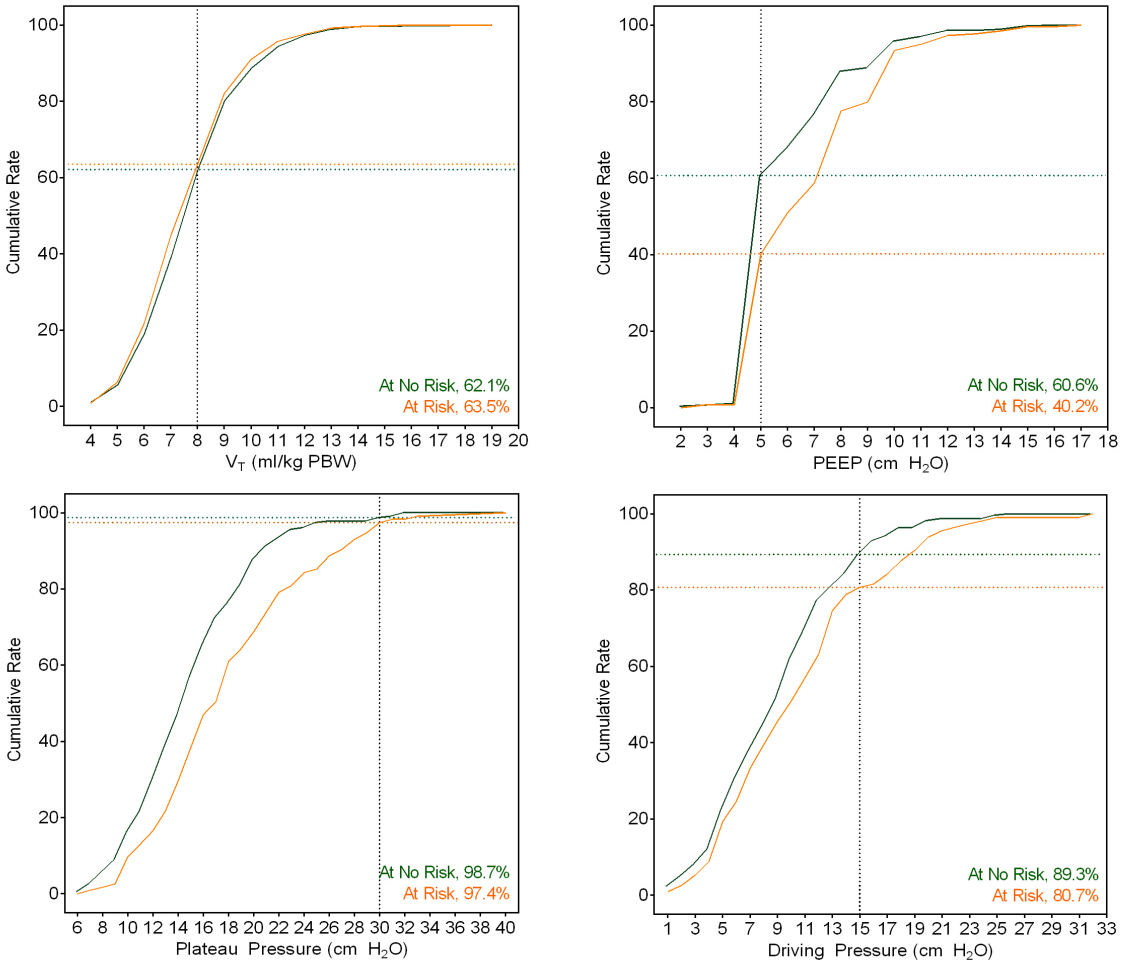
Cumulative Rate
V_T (ml/kg PBW)
At No Risk, 62.1%
At Risk, 63.5%
PEEP (cm H_2O)
At No Risk, 60.6%
At Risk, 40.2%
Plateau Pressure (cm H_2O)
At No Risk, 98.7%
At Risk, 97.4%
Driving Pressure (cm H_2O)
At No Risk, 89.3%
At Risk, 80.7%

FIGURE 2

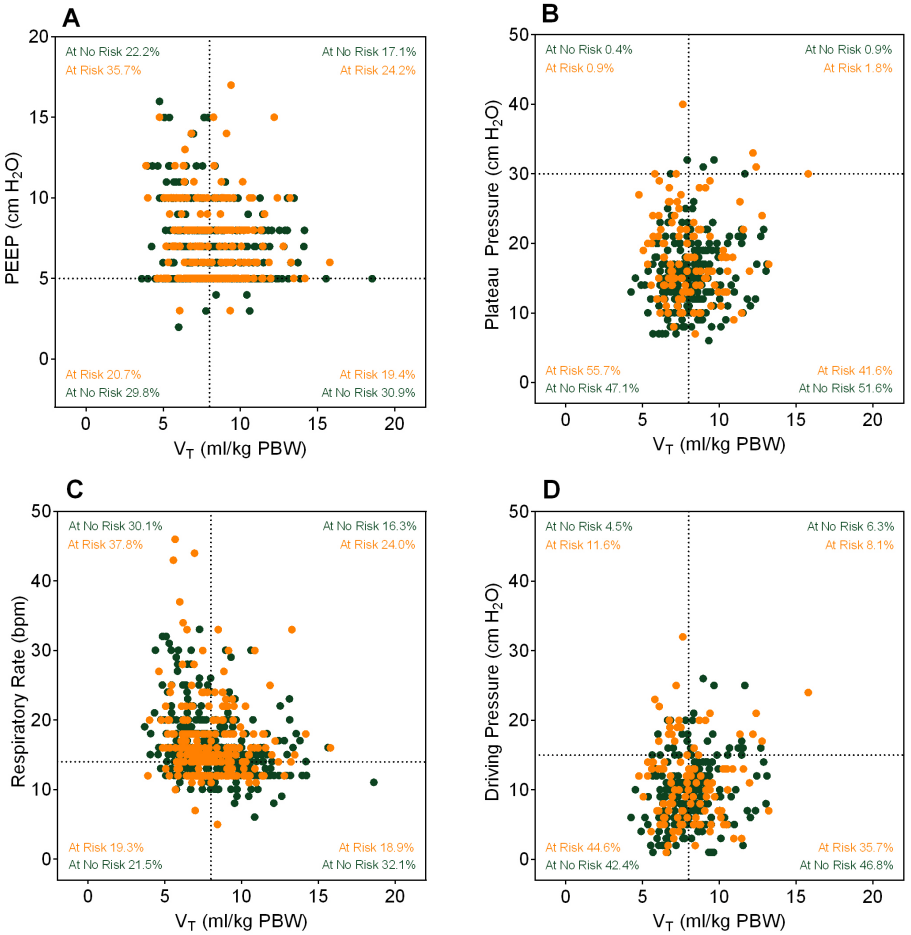
A
At No Risk 22.2%
At Risk 35.7%
At No Risk 17.1%
At Risk 24.2%
At Risk 20.7%
At No Risk 29.8%
At Risk 19.4%
At No Risk 30.9%
PEEP (cm H2O)
VT (ml/kg PBW)
B
At No Risk 0.4%
At Risk 0.9%
At No Risk 0.9%
At Risk 1.8%
At Risk 55.7%
At No Risk 47.1%
At Risk 41.6%
At No Risk 51.6%
Plateau Pressure (cm H2O)
VT (ml/kg PBW)
C
At No Risk 30.1%
At Risk 37.8%
At No Risk 16.3%
At Risk 24.0%
At Risk 19.3%
At No Risk 21.5%
At Risk 18.9%
At No Risk 32.1%
Respiratory Rate (bpm)
VT (ml/kg PBW)
D
At No Risk 4.5%
At Risk 11.6%
At No Risk 6.3%
At Risk 8.1%
At Risk 44.6%
At No Risk 42.4%
At Risk 35.7%
At No Risk 46.8%
Driving Pressure (cm H2O)
VT (ml/kg PBW)

FIGURE 3

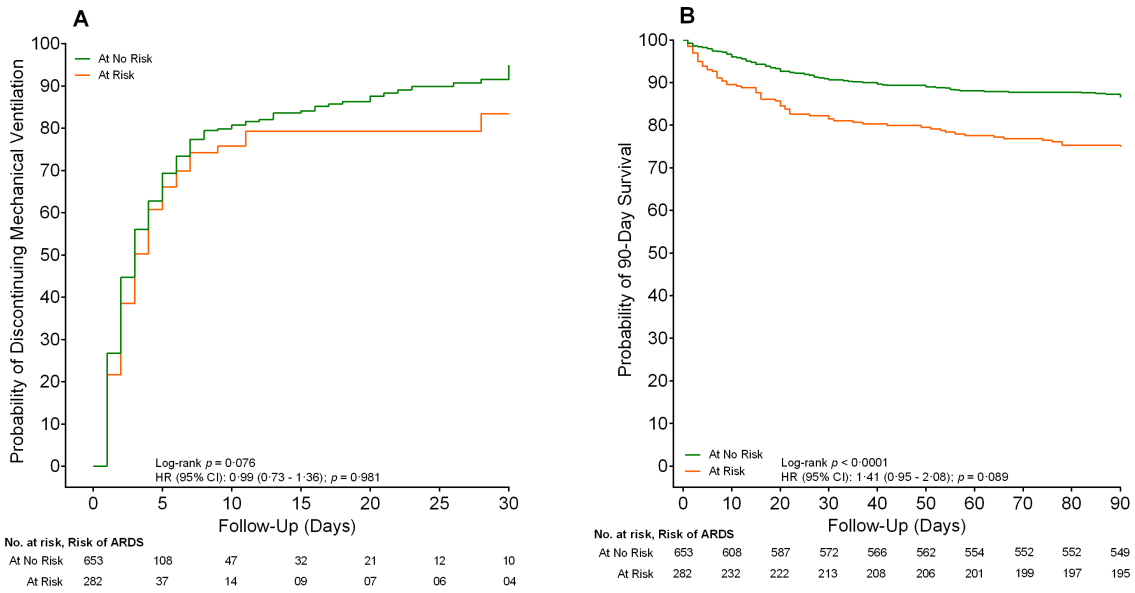
A
Probability of Discontinuing Mechanical Ventilation
At No Risk
At Risk
Log-rank p = 0·076
HR (95% CI): 0·99 (0·73 - 1·36); p = 0·981
Follow-Up (Days)
No. at risk, Risk of ARDS
At No Risk 653 108 47 32 21 12 10
At Risk 282 37 14 09 07 06 04
B
Probability of 90-Day Survival
At No Risk
At Risk
Log-rank p < 0·0001
HR (95% CI): 1·41 (0·95 - 2·08); p = 0·089
Follow-Up (Days)
No. at risk, Risk of ARDS
At No Risk 653 608 587 572 566 562 554 552 552 549
At Risk 282 232 222 213 208 206 201 199 197 195

FIGURE 4

Table 1 – Baseline characteristics of critically ill patients by risk of ARDS

	All (*n* = 935)	At Risk (*n* = 282)	At No Risk (*n* = 653)	*p* value[a]
Age, years	65·0 (52·0 – 75·0)	65·0 (50·7 – 75·0)	65·0 (53·0 – 74·0)	0·674
Gender, male	62·6 (570 / 910)	62·8 (177 / 282)	62·6 (393 / 628)	0·957
Ethnic	1·2 (11 / 903)	0·4 (1 / 282)	1·6 (10 / 621)	
African	1·2 (11 / 903)	2·1 6 / 282)	0·8 (5 / 621)	
Afro-Caribbean	6·3 (57 / 903)	10·3 (29 / 282)	4·5 (28 / 621)	0·002
Asian	84·2 (760 / 903)	79·1 (223 / 282)	86·5 (537 / 621)	
Caucasian	7·1 (64 / 903)	8·2 (23 / 282)	6·6 (41 / 621)	
Latin American				
BMI, kg/m^2	25·5 (22·9 – 29·2)	26·0 (23·4 – 30·2)	25·3 (22·7 – 28·8)	0·009
PBW, kg	64·2 (54·2 – 71·5)	66·0 (54·2 – 71·5)	64·2 (54·2 – 71·5)	0·971
Smoker				
Never	33·0 (298 / 902)	28·7 (81 / 282)	35·0 (217 / 620)	
Previous	17·0 (153 / 902)	16·7 (47 / 282)	17·1 (106 / 620)	
Former	3·4 (31 / 902)	4·3 (12 / 282)	3·1 (19 / 620)	0·229
Current	19·3 (174 / 902)	22·7 (64 / 282)	17·7 (110 / 620)	
Unknown	27·3 (246 / 902)	27·7 (78 / 282)	27·1 (168 / 620)	
Functional status				
Independent	75·0 (675 / 900)	66·7 (188 / 282)	78·8 (487 / 618)	
Partially dependent	17·6 (158 / 900)	23·0 (65 / 282)	15·0 (93 / 618)	0·0002
Totally dependent	4·4 (40 / 900)	7·4 (21 / 282)	3·1 (19 / 618)	
Unknown	3·0 (27 / 900)	2·8 (8 / 282)	3·1 (19 / 618)	
Reason for ICU admission				
Planned surgery	34·7 (313 / 902)	6·8 (19 / 281)	47·3 (294 / 621)	
Emergency surgery	20·7 (187 / 902)	31·7 (89 / 281)	15·8 (98 / 621)	< 0·0001
Clinical condition	44·6 (402 / 902)	61·6 (173 / 281)	36·9 (229 / 621)	
NIV before intubation	7·7 (69 / 900)	15·2 (43 / 282)	4·2 (26 / 618)	< 0·0001
Duration, minutes	240·0 (75·0 – 720·0)	159·0 (60·0 – 1050·0)	240·0 (120·0 – 555·0)	< 0·0001
Risk of death*, %	12·7 (7·0 – 35·1)	29·4 (11·6 – 49·7)	12·0 (3·0 – 30·0)	< 0·0001
LIPS	3·5 (2·0 – 6·0)	6·5 (5·5 – 8·5)	2·5 (1·0 – 3·5)	< 0·0001
Limitation of treatment	3·4 (30 / 892)	6·1 (17 / 279)	2·1 (13 / 613)	0·002
Unplanned admission	53·7 (483 / 900)	74·4 (209 / 281)	44·3 (274 / 619)	< 0·0001
Reason for intubation*				
Cardiac arrest	8·8 (79 / 900)	10·3 (29 / 282)	8·1 (50 / 618)	0·280
Anesthesia for surgery (planned)	51·9 (467 / 900)	31·2 (88 / 282)	61·4 (379 / 618)	< 0·0001
Depressed level of consciousness	26·6 (239 / 900)	31·9 (90 / 282)	24·1 (149 / 618)	0·014
Respiratory failure	28·4 (255 / 900)	54·3 (153 / 282)	16·6 (102 / 618)	< 0·0001
Chronic co-morbidity*				
Hypertension	42·6 (381 / 894)	39·5 (111 / 281)	44·0 (270 / 613)	0·202
Diabetes mellitus	18·5 (166 / 896)	15·3 (43 / 281)	20·0 (123 / 615)	0·093
Heart failure	17·7 (158 / 894)	18·5 (52 / 281)	17·3 (106 / 613)	0·658
Chronic kidney failure	10·5 (94 / 897)	12·8 (36 / 281)	9·4 (58 / 616)	0·123
Cirrhosis	3·7 (33 / 896)	3·9 (11 / 281)	3·6 (22 / 615)	0·803
COPD	12·0 (107 / 888)	17·9 (50 / 281)	9·4 (57 / 608)	0·0003
Oxygen at home	1·7 (16 / 935)	2·8 (8 / 282)	1·2 (8 / 653)	0·081
Cancer	24·4 (219 / 896)	16·0 (45 / 281)	28·3 (174 / 615)	< 0·0001
Former	7·3 (65 / 888)	5·4 (15 / 277)	8·2 (50 / 611)	0·0001
Current	16·4 (146 / 888)	9·4 (26 / 277)	19·6 (120 / 611)	
Neuromuscular disease	2·1 (19 / 895)	1·8 (5 / 281)	3·1 (19 / 614)	0·750
Immunosuppression	7·8 (70 / 895)	7·8 (22 / 281)	7·5 (46 / 612)	0·995
Use of NIV at home	1·2 (11 / 892)	1·8 (5 / 280)	1·0 (6 / 612)	0·311
Severity of illness, SOFA score[b]				
Total	6·0 (4·0 – 9·0)	8·0 (5·0 – 11·0)	5·0 (3·0 – 8·0)	< 0·0001
Pulmonary	2·0 (0·0 – 3·0)	2·0 (1·0 – 3·0)	1·0 (0·0 – 2·0)	< 0·0001
Hematologic	0·0 (0·0 – 1·0)	0·0 (0·0 – 1·0)	0·0 (0·0 – 1·0)	0·484
Liver	0·0 (0·0 – 0·0)	0·0 (0·0 – 1·0)	0·0 (0·0 – 0·0)	0·026
Circulation	1·0 (0·0 – 3·0)	2·0 (0·0 – 4·0)	0·0 (0·0 – 3·0)	< 0·0001
Neurology	2·0 (0·0 – 4·0)	3·0 (1·0 – 4·0)	2·0 (0·0 – 4·0)	< 0·0001
Renal	0·0 (0·0 – 1·0)	0·0 (0·0 – 1·0)	0·0 (0·0 – 1·0)	< 0·0001

ARDS: acute respiratory distress syndrome; SOFA: Sequential Organ Failure Assessment; COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Failure; LIPS: Lung Injury Prediction Score; NIV: non-invasive ventilation

*: patient can have more than one diagnosis

a: *p* value represents comparison between risk categories for each variable

b: for all SOFA scores for which data points were missing, this value was omitted and the denominator adjusted accordingly

Table 2 – Characteristics of critically ill patients treated with invasive ventilation by risk of ARDS

	All (*n* = 935)	At Risk (*n* = 282)	At No Risk (*n* = 653)	*p* value[a]
Ventilator settings				
Mode of ventilation				
Volume-controlled	13·7 (116 / 849)	16·7 (44 / 264)	12·3 (72 / 585)	
Pressure-controlled	22·7 (193 / 849)	22·3 (59 / 264)	22·9 (134 / 585)	
Pressure support	9·4 (80 / 849)	8·0 (21 / 264)	10·1 (59 / 585)	
SIMV	26·3 (223 / 849)	29·5 (78 / 264)	24·8 (145 / 585)	
BiPAP / APRV	21·8 (185 / 849)	20·5 (54 / 264)	22·4 (131 / 585)	
ASV	2·0 (17 / 849)	0·4 (1 / 264)	2·7 (16 / 585)	0·111
PAV	0·0 (0 / 849)	0·0 (0 / 264)	0·0 (0 / 585)	
NAVA	0·1 (1 / 849)	0·0 (0 / 264)	0·2 (1 / 585)	
VAPS	0·9 (8 / 849)	1·1 (3 / 264)	0·9 (5 / 585)	
PRVC	2·7 (23 / 849)	1·5 (4 / 264)	3·2 (19 / 585)	
Other	0·4 (3 / 849)	0·0 (0 / 264)	0·5 (3 / 585)	
Ventilatory parameters				
Peak pressure, cmH_2O	20·0 (17·0 – 24·0)	22·0 (19·0 – 27·0)	19·0 (16·0 – 22·0)	< 0·0001
Plateau pressure, cmH_2O[b]	16·0 (13·0 – 20·0)	17·0 (14·0 – 22·0)	15·0 (12·0 – 18·0)	< 0·0001
No of patients	36·7 (343 / 935)	40·8 (115 / 282)	34·9 (228 / 653)	0·100
Tidal volume, milliliters	500 (440 – 575)	500 (427 – 571)	500 (449 – 580)	0·166
Tidal volume, ml/kg PBW	7·9 (6·8 – 9·1)	7·6 (6·7 – 9·1)	7·9 (6·8 – 9·1)	0·346
Control vent mode	7·7 (6·7 – 8·9)	7·6 (6·6 – 9·0)	7·8 (6·8 – 8·9)	0·550
Spontaneous vent mode	8·0 (6·8 – 9·2)	7·8 (6·8 – 9·1)	8·0 (6·8 – 9·3)	0·491
p value	0·089	0·330	0·165	
≤ 7	29·8 (242 / 811)	33·7 (86 / 255)	28·1 (156 / 556)	
7 – 8	42·8 (347 / 811)	38·0 (97 / 255)	45·0 (250 / 556)	0·142
9 – 10	19·9 (161 / 811)	22·0 (56 / 255)	18·9 (105 / 556)	
> 10	7·5 (61 / 811)	6·3 (16 / 255)	8·1 (45 / 556)	
PEEP, cmH_2O	5·0 (5·0 – 8·0)	6·0 (5·0 – 8·0)	5·0 (5·0 – 7·0)	< 0·0001
≤ 5	54·2 (450 / 830)	40·2 (104 / 259)	60·6 (346 / 571)	
6 – 8	30·5 (253 / 830)	37·5 (97 / 259)	27·3 (156 / 571)	< 0·0001
9 – 10	10·4 (86 / 830)	15·8 (41 / 259)	7·9 (45 / 571)	
> 10	4·9 (41 / 830)	6·6 (17 / 259)	4·2 (24 / 571)	
Driving pressure, cmH_2O	10·0 (6·0 – 13·0)	10·0 (6·7 – 14·0)	9·0 (6·0 – 12·0)	0·048
No of patients	36·2 (339 / 935)	40·4 (114 / 282)	34·4 (225 / 653)	0·093
Respiratory rate, bpm	15·0 (12·0 – 18·0)	16·0 (14·0 – 18·0)	14·0 (12·0 – 16·0)	< 0·0001
FiO_2	0·5 (0·4 – 0·6)	0·5 (0·4 – 0·7)	0·4 (0·4 – 0·5)	< 0·0001
Static compliance, ml/cmH_2O	54·2 (36·9 – 77·1)	52·5 (32·2 – 74·4)	56·0 (40·9 – 84·2)	0·050
Minute-Ventilation, l/min	7·4 (6·2 – 8·9)	7·6 (6·5 – 9·6)	7·2 (6·1 – 8·7)	0·005
Laboratory data				
Laboratory parameters				
PaO_2 / FiO_2, mmHg	261 (165 – 367)	201 (129 – 300)	310 (210 – 405)	< 0·0001
$PaCO_2$, mmHg	38·0 (34·0 – 45·0)	42·0 (37·0 – 52·5)	37·5 (33·0 – 45·0)	< 0·0001
pH	7·36 (7·30 – 7·42)	7·34 (7·26 – 7·41)	7·38 (7·32 – 7·43)	< 0·0001
HCO_3, mEq/liter	22·0 (20·0 – 25·0)	22·0 (19·0 – 26·0)	22·0 (20·0 – 25·0)	0·181

ARDS: acute respiratory distress syndrome; LIPS: Lung Injury Prediction Score; SIMV: synchronized intermittent mandatory ventilation; BiPAP: biphasic positive airway pressure; APRV: airway pressure release ventilation; ASV: adaptive support ventilation; PAV: proportional assist ventilation; NAVA: neurally adjusted ventilatory assist; VAPS: volume-assured pressure support; PRVC: pressure regulated volume control; PEEP: positive end-expiratory pressure, FiO_2: inspired fraction of oxygen; PaO_2: partial pressure of oxygen; $PaCO_2$: partial pressure of carbon dioxide; HCO_3: bicarbonate; PBW: predicted body weight; BPM: beats per minute

a: *p* value represents comparison between risk categories for each variable

b: plateau pressure values are limited to patients in whom this value was reported and in whom either an assist control mode was used or in whom a mode permitting spontaneous ventilation was used

Table 3 – Comparison of ventilatory parameters in patients who developed or not ARDS during the follow-up

	Patients at Risk of ARDS (*n* = 282)			Patients at No Risk of ARDS (*n* = 653)		
	Patients Who Developed ARDS (*n* = 19)	Patients Who Did Not Develop ARDS (*n* = 263)	*p* value	Patients Who Developed ARDS (*n* = 17)	Patients Who Did Not Develop ARDS (*n* = 636)	*p* value
Tidal volume, ml/kg PBW	7·6 (6·1 – 9·1)	7·7 (6·8 – 9·1)	0·471	7·5 (6·2 – 8·3)	7·9 (6·8 – 9·1)	0·323
Plateau pressure, cmH_2O	19·0 (11·0 – 29·0)	17·0 (14·0 – 21·2)	0·487	20·0 (11·0 – 27·5)	15·0 (12·0 – 18·0)	0·227
Driving pressure, cmH_2O	11·0 (6·0 – 18·0)	10·0 (6·5 – 13·5)	0·669	13·5 (5·2 – 22·5)	9·0 (6·0 – 12·0)	0·257
PEEP, cmH_2O	6·0 (5·0 – 10·0)	6·0 (5·0 – 8·0)	0·973	5·0 (5·0 – 8·0)	5·0 (5·0 – 7·0)	0·608
FiO_2, %	0·6 (0·5 – 0·9)	0·5 (0·4 – 0·7)	0·022	0·5 (0·4 – 0·9)	0·4 (0·4 – 0·5)	0·048
Respiratory rate, bpm	17·0 (13·0 – 18·0)	16·0 (14·0 – 18·0)	0·699	14·0 (14·0 – 18·0)	14·0 (12·0 – 16·0)	0·505

ARDS: acute respiratory distress syndrome; PBW: predicted body weight; PEEP: positive end-expiratory pressure; FiO_2: fraction of inspired oxygen

Table 4 – Outcomes of invasively ventilated critically ill by risk of ARDS

	All (*n* = 935)	At Risk (*n* = 282)	At No Risk (*n* = 653)	*p* value[a]	Adjusted HR (95% CI)[b]	*p* value
Pulmonary Complications						
Total	27·2 (222 / 816)	35·4 (92 / 260)	23·4 (130 / 556)	0·0003	1·42 (1·05 – 1·91)	0·021
Pneumonia	10·7 (85 / 816)	14·1 (36 / 260)	9·0 (49 / 556)	0·029	1·57 (0·98 – 2·53)	0·060
ARDS	4·6 (36 / 816)	7·7 (19 / 260)	3·2 (17 / 556)	0·004	1·88 (0·92 – 3·84)	0·082
Mild	1·3 (10 / 816)	1·6 (4 / 260)	1·1 (6 / 556)			
Moderate	2·7 (21 / 816)	5·2 (13 / 260)	1·5 (8 / 556)	0·020	---	---
Severe	0·6 (5 / 816)	0·8 (2 / 260)	0·6 (3 / 556)			
Pneumothorax	1·4 (11 / 816)	1·6 (4 / 260)	1·3 (7 / 556)	0·729	1·33 (0·46 – 3·84)	0·595
Pleural effusion	9·5 (74 / 816)	13·0 (32 / 260)	7·8 (42 / 556)	0·021	1·42 (0·78 – 2·60)	0·250
Atelectasis	8·5 (67 / 816)	9·3 (23 / 260)	8·1 (44 / 556)	0·571	0·77 (0·36 – 1·64)	0·493
Cardiogenic pulmonary oedema	1·9 (15 / 816)	3·6 (9 / 260)	1·1 (6 / 556)	0·016	1·74 (0·36 – 8·36)	0·488
New pulmonary infiltrates	2·2 (17 / 816)	3·6 (9 / 260)	1·5 (8 / 556)	0·056	2·31 (0·70 – 7·59)	0·168
Extra-Pulmonary Complications						
Acute kidney injury	19·0 (152 / 798)	29·8 (74 / 248)	14·2 (78 / 550)	< 0·0001	1·42 (0·98 – 2·04)	0·062
Risk	4·5 (36 / 798)	8·1 (20 / 248)	2·9 (16 / 550)			
Injury	4·9 (39 / 798)	7·3 (18 / 248)	3·8 (21 / 550)			
Failure	7·1 (57 / 798)	11·3 (28 / 248)	5·3 (29 / 550)	< 0·0001	---	---
Loss	1·3 (10 / 798)	1·2 (3 / 248)	1·3 (7 / 550)			
End-stage	1·3 (10 / 798)	2·0 (5 / 248)	0·9 (5 / 550)			
Renal replacement therapy	4·4 (35 / 798)	6·0 (15 / 248)	3·6 (20 / 550)	0·129	1·33 (0·61 – 2·92)	0·472
Extra-pulmonary infection	8·5 (68 / 798)	12·3 (31 / 248)	6·8 (37 / 550)	0·008	1·96 (1·11 – 3·44)	0·019
Length of Stay						
ICU, days						
All patients	4·0 (2·0 – 10·0)	7·0 (4·0 – 16·0)	3·0 (2·0 – 7·0)	< 0·0001	4·23 (1·82 – 6·63)[d]	0·001
Surviving patients	4·0 (2·0 – 9·0)	7·0 (4·0 – 16·0)	3·0 (2·0 – 6·0)	< 0·0001	3·85 (1·23 – 6·48) [d]	0·004
Hospital, days						
All patients	16·5 (9·0 – 35·0)	22·0 (11·0 – 46·0)	14·0 (8·0 – 30·0)	0·0002	3·88 (-1·35 – 9·11) [d]	0·146
Surviving patients	17·0 (9·0 – 35·0)	27·0 (14·0 – 53·0)	14·0 (8·0 – 30·0)	< 0·0001	4·93 (-1·38 – 11·23) [d]	0·126
Mechanical Ventilation						
Tracheostomy	6·9 (54 / 785)	11·3 (27 / 240)	5·0 (27 / 545)	0·001	0·80 (0·49 – 1·31)	0·374
Duration of ventilation						
All patients	2·0 (1·0 – 4·0)	2·0 (1·0 – 4·0)	2·0 (1·0 – 4·0)	0·198	-0·19 (-1·59 – 1·22)[d]	0·792
Surviving patients	2·0 (1·0 – 4·0)	2·0 (1·0 – 4·0)	2·0 (1·0 – 4·0)	0·203	-1·23 (-2·53 – 0·06)[d]	0·063
Ventilator-free days at day 28[c]	25·0 (14·7 – 27·0)	24·0 (0·0 – 27·0)	25·0 (21·0 – 27·0)	0·002	---	---
Mortality						
ICU	16·8 (128 / 760)	29·1 (66 / 227)	11·6 (62 / 533)	< 0·0001	1·23 (0·71 – 2·11)	0·462
Hospital	20·6 (160 / 775)	31·9 (74 / 232)	15·8 (86 / 543)	< 0·0001	0·95 (0·64 – 1·41)	0·806
90-Day	21·1 (197 /	31·2 (88 /	16·7 (109 /	<	1·41 (0·95 – 2·08)	0·089

	935)	282)	653)	0·0001

ARDS: acute respiratory distress syndrome; ICU: intensive care unit; HR: hazard ratio; CI: confidence interval
a: *p* value represents comparison between risk categories for each variable
b: frailty model adjusted for BMI, functional status, risk of death and SOFA total at baseline
c: in patients in whom death occurs while receiving invasive mechanical ventilation, invasive ventilation-free days are counted as 0
d: coefficient of a multi-level linear regression

EPIDEMIOLOGY, PRACTICE OF VENTILATION AND OUTCOME FOR PATIENTS AT RISK OF ARDS IN INTENSIVE CARE UNITS IN 16 COUNTRIES

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eTable 1 – Definitions of pulmonary complications

Complication	Definition
ARDS	According to the Berlin criteria
Pneumonia	Defined as need of new antibiotics in the presence of new or changed lung opacities on chest X-ray and/or new or changed sputum plus at least one of the following criteria: 1) temperature > 38·3 ºC; or 2) WBC count > 12,000
Pneumothorax	Defined as the air in mediastinum or in the pleural space with no vascular bed surrounding the visceral pleura
Pleural effusion	Suggested by lung opacification with shift of the mediastinum, hilum, or hemidiaphragm towards the non-affected area
Atelectasis	Suggested by lung opacification with shift of the mediastinum, hilum, or hemidiaphragm towards the affected area, and compensatory overinflation in the adjacent nonatelectatic lung
Cardiogenic pulmonary oedema	Defined as pulmonary edema due to cardiac failure
New pulmonary infiltrates	Defined as infiltrates on the CXR without other clinical signs

ARDS: acute respiratory distress syndrome

Berlin criteria: Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al· Acute respiratory distress syndrome: the Berlin Definition· JAMA 2012;307:2526-2533·

eTable 2 – Full list of participating centers

Country	City	Institution	Number of Patients
Australia	Canberra	Canberra Hospital	9
Australia	Melbourne	St Vincent's Hospital Melbourne	16
Australia	Sidney	Concord Hospital	9
Austria	Vienna	Vienna General Hospital	13
Belgium	Leuven	UZ Leuven	11
Belgium	Brugge	AZ Sint-Jan Brugge-Oostende AV	8
Belgium	Gent	Ghent University Hospital	8
Brazil	São Paulo	Hospital Israelita Albert Einstein	19
Brazil	Pouso Alegre	Hospital Renascentista	1
Brazil	Montenegro	Hospital Montenegro	8
Brazil	Vitória	Hospital Vitória Apart	3
Brazil	Porto Alegre	Hospital Nossa Senhora da Conceição	13
Brazil	Porto Alegre	Hospital Moinhos de Ventos	5
Brazil	São José dos Campos	Hospital Vivalle	5
Brazil	Florianópolis	Hospital Nereu Ramos	20
Brazil	Taguatinga	Hospital Alvorada Taguatinga	1
Brazil	Campo Grande	Universidade Federal de Mato Grosso do Sul	10
Brazil	São Paulo	Universidade Federal de São Paulo – Escola Paulista de Medicina	14
Brazil	São Paulo	Hospital do Coração	10
Brazil	Bragança Paulista	Hospital Universitário São Francisco	4
Brazil	Vitória	Hospital UNIMED Vitória	4
Chile	Santiago	Hospital Santiago Oriente – Dr Luis Tisné Brousse	2
Chile	Punta Arenas	Hospital Clinico Magallanes	5
Chile	Viña Del Mar	Hospital Dr Gustavo Fricke	1
Croatia	Zagreb	Clinical Hospital Dubrava	30
Croatia	Osijek	University of Osijek	9
Croatia	Zagreb	University Hospital Merkur	20
Croatia	Slavonski Brod	'Dr Josip Bencevic' General Hospital	5
Croatia	Split	Split University Hospital Center	15
Croatia	Zadar	General Hospital Zadar	5
Czech Republic	Brno	University Hospital Brno – Medical Faculty of Msaryk University	18
Czech Republic	Ostrava	University Hospital Ostrava	4
Germany	Leipzig	University Hospital Leipzig	19
Germany	Dusseldorf	University Hospital Dusseldorf	46
Ireland	Galway	Galway University Hospital	13
Ireland	Dublin	St James's Hospital	10
Ireland	Cork	Cork University Hospital	8
Italy	San Giovanni Rotondo	IRCCS 'Casa Sollievo Della Sofferenza	8
Italy	Palermo	Policlinico P Giaccone – University of Palermo	9
Italy	Lecce	Vito Fazzi Hospital	19
Italy	Ferrara	Università Degli Studi di Ferrara	9
Italy	Brescia	Spedali Civili di Brescia – University of Brescia	8
Italy	Sassari	Sassari University Hospital	4
Italy	Foggia	Ospedali Riuniti – University of Foggia	18
Italy	Genoa	IRCCS San Martino – University of Genoa	13
Italy	Varese	Insubria University of Varese	15
Italy	Monopoli	ASL Bari – Monopoli Hospital	3
Kosovo	Prishtina	University Clincal Center of Kosovo	6
Netherlands	Amsterdam	University of Amsterdam – Academic Medical Center	25
Netherlands	Amsterdam	VU University Medical Center	28
Netherlands	Leiden	Leiden University Medical Center	27
Netherlands	Leeuwarden	Medisch Centrum Leeuwarden	19
Turkey	Izmir	Tepecik Training and Research Hospital	20
Turkey	Erzurum	Ataturk University	1
Turkey	Manisa	Celal Bayar University	5
Turkey	Gaziantep	Ozel Primer Hospital	6
Turkey	Kirikkale	Kirikkale University	1
Turkey	Instanbul	Fatih Sultan Mehmet Egitim ve Arastirma Hastanesi	11
Turkey	Instanbul	Instabul Medicine Faculty	19
Turkey	Instanbul	Haydarpasa Numune Egitim ve Arastirma Hastanesi	8
Turkey	Instanbul	Kanuni Education and Training Hospital	2
Turkey	Bakirkoy	Bakirkoy Dr Sadi Konuk Egitim ve Arastirma Hastanesi	6
Turkey	Samsun	Ondokuz Mayis University	6
Turkey	Trabzon	Karadeniz Teknik University	2
Turkey	Van	Yüzüncü Yil University	16
Turkey	Çanakkale	Çanakkale Onsekiz Mart University	2
Turkey	Merkez	Mardin Devlet Hastanesi	4
Turkey	Bursa	Uludag University Faculty of Medicine	9
United Kingdom	Sheffield	Sheffield Teaching Hospital	11
United Kingdom	Liverpool	Aintree University Hospital NHS Foundation Trust	5

United Kingdom	Manchester	Central Manchester University Hospital	9
United Kingdom	Gloucester	Gloucestershire Hospitals NHS Trust	2
United Kingdom	Wakefield	The Mid Yorkshire Hospitals NHS Trust	5
United Kingdom	Milton Keynes	Milton Keynes Hospital NHS Foundation Trust	8
United Kingdom	Hartlepool	North Tees and Hartlepool NHS Foundation Trust	2
United Kingdom	Salford	Salford Royal NHS Foundation Trust	7
United Kingdom	Torquay	South Devon Healthcare NHS Foundation Trust	3
United Kingdom	Middlesbrough	South Tees Hospital NHS Foundation Trust	14
United Kingdom	Manchester	University Hospitals of South Manchester NHS Foundation Trust	1
United Kingdom	Chertsey	Ashford and St Peters Hospital NHS Foundation Trust	8
United Kingdom	Basingstoke	Basingstoke and North Hampshire NHS Foundation	10
United Kingdom	Bristol	Bristol Royal Infirmary	3
United Kingdom	Darlington	County Durham and Darlington NHS Foundation Trust	1
United Kingdom	Derby	Derby Hospitals NHS Foundation Trust	4
United Kingdom	Dorchester	Dorset County Hospital	1
United Kingdom	East Sussex	East Sussex Healthcare Trust	9
United Kingdom	Gateshead	Gateshead Health NHS Foundation Trust	3
United Kingdom	Swindon	Great Western Hospital	1
United Kingdom	Ipswich	Ipswich Hospital NHS Trust	3
United Kingdom	Great yarmouth	James Paget University Hospital NHS Foundation Trust	2
United Kingdom	London	Kings College Hospital	21
United Kingdom	Gillingham	Medway NHS Foundation Trust	3
United Kingdom	Newcastle Upon Tyne	The Newcastle Upon Tyne Hospitals NHS Foundation Trust	7
United Kingdom	Hensingham	North Cumbria University Hospitals NHS Trust	1
United Kingdom	Barnstaple	North Devon Healthcare NHS Trust	1
United Kingdom	Stoke on Trent	University Hospital of North Staffordshire NHS Trust	6
United Kingdom	Poole	Poole Hospital NHS Foundation Trust	5
United Kingdom	Portsmouth	Portsmouth Hospital NHS Trust	11
United Kingdom	East Grinstead	Queen Victoria Hospital NHS Foundation Trust	3
United Kingdom	Rotherham	The Rotherham NHS Foundation Trust	2
United Kingdom	Truro	Royal Cornwall Hospital	2
United Kingdom	Liverpool	Royal Liverpool and Broadgreen University Hospitals NHS Trust	6
United Kingdom	Shrewsbury	Royal Shrewsbury Hospitals NHS Trust	6
United Kingdom	Guildford	Royal Surrey County Hospital NHS Foundation Trust	7
United Kingdom	Brighton	Royal Sussex County Hospital	5
United Kingdom	Wolverhampton	The Royal Wolverhampton NHS Trust	3
United Kingdom	South Sheilds	South Tyneside NHS Foundation Trust	2
United Kingdom	London	St Georges Hospital London	22
United Kingdom	Sunderland	City Hospitals Sunderland NHS Foundation Trust	1
United Kingdom	Liverpool	The Walton Centre NHS Foundation Trust	3
United Kingdom	Cambridge	Cambridge University Hospitals NHS Foundation (Addenbrookes)	5
United Kingdom	Chesterfield	Chesterfield Royal Hospital NHS Foundation Trust	6
United Kingdom	Colchester	Colchester Hospital University NHS Foundation Trust	3
United Kingdom	Chester	Countess of Chester Hospital NHS Foundation Trust	5
United Kingdom	Plymouth	Plymouth Hospitals NHS Trust	13
United Kingdom	Sutton-in-Ashfield	Sherwood Forest Hospitals NHS Foundation Trust	4
United Kingdom	Wirral	Wirral University Teaching Hospital NHS Foundation Trust	6
Uruguay	Montevideo	Hospital de Clinicas	6
United States of America	Boston	Massachusetts General Hospital	14

eTable 3 – Geographic distribution of participating ICUs and enrolled patients

	Participating ICUs (*n*)	Enrolled Patients (*n*)
Europe	**97**	**842**
Austria	1	13
Belgium	3	27
Croatia	6	84
Czech Republic	2	22
Germany	2	65
Ireland	3	31
Italy	10	106
Kosovo	1	6
Netherlands	4	99
Turkey	16	118
United Kingdom	49	271
North America	**1**	**14**
United States	1	14
Oceania	**3**	**34**
Australia	3	34
South America	**18**	**131**
Brazil	14	117
Chile	3	8
Uruguay	1	6
TOTAL	**119**	**1,021**

eTable 4 – Baseline characteristics of critically ill patients by risk of ARDS

	All (*n* = 935)	At Risk (*n* = 282)	At No Risk (*n* = 653)	*p* value[a]
Reason for Intubation[*]				
Depressed level of consciousness	26·6 (239 / 899)	31·9 (90 / 282)	24·1 (149 / 617)	0·014
Stroke	3·3 (30 / 897)	4·3 (12 / 281)	2·9 (18 / 616)	
Intracranial bleeding	2·1 (19 / 897)	1·8 (5 / 281)	2·3 (14 / 616)	
Subarachnoid hemorrhage	1·9 (17 / 897)	2·5 (7 / 281)	1·6 (10 / 616)	
Traumatic brain injury	4·8 (43 / 897)	8·2 (23 / 281)	3·2 (20 / 616)	
Meningo-encephalitis	1·2 (11 / 897)	1·1 (3 / 281)	1·3 (8 / 616)	
Metabolic / Hepatic encephalopathy	3·1 (28 / 897)	3·9 (11 / 281)	2·8 (17 / 616)	0·030
Intoxication	3·6 (32 / 897)	2·5 (7 / 281)	4·1 (25 / 616)	
Status epilepticus	1·2 (11 / 897)	1·1 (3 / 281)	1·3 (8 / 616)	
Hypercapnic coma	0·8 (7 / 897)	1·8 (5 / 281)	0·3 (2 / 616)	
Hypoxic-ischemic encephalopathy	0·8 (7 / 897)	1·1 (3 / 281)	0·6 (4 / 616)	
Other	3·5 (31 / 897)	3·2 (9 / 281)	3·6 (22 / 616)	
Respiratory Failure	28·4 (255 / 898)	54·3 (153 / 282)	16·6 (102 / 616)	< 0·0001
Community-Acquired Pneumonia	3·8 (34 / 898)	7·1 (20 / 282)	2·3 (14 / 616)	
Nosocomial Pneumonia	3·1 (28 / 898)	6·7 (19 / 282)	1·5 (9 / 616)	
Post-surgery (unplanned)	4·7 (42 / 898)	7·1 (20 / 282)	3·6 (22 / 616)	
Cardiogenic pulmonary edema	3·1 (28 / 898)	7·1 (20 / 282)	1·3 (8 / 616)	
Extra-pulmonary sepsis	4·3 (39 / 898)	9·9 (28 / 282)	1·8 (11 / 616)	
COPD exacerbation	2·4 (22 / 898)	3·5 (10 / 282)	1·9 (12 / 616)	< 0·0001
Aspiration	0·7 (6 / 898)	1·8 (5 / 282)	0·2 (1 / 616)	
Pulmonary contusion	0·9 (8 / 898)	2·8 (8 / 282)	0·0 (0 / 616)	
Pulmonary embolism	0·6 (5 / 898)	0·7 (2 / 282)	0·5 (3 / 616)	
Decrease of vital capacity	0·4 (4 / 898)	0·4 (1 / 282)	0·5 (3 / 616)	
Other	4·2 (38 / 898)	7·1 (20 / 282)	2·9 (18 / 616)	
Chronic co-morbidity[*]				
Diabetes mellitus	18·5 (166 / 896)	15·3 (43 / 281)	20·0 (123 / 615)	0·093
Insulin	6·1 (54 / 892)	5·7 (16 / 281)	6·2 (38 / 611)	
Oral medication	11·4 (102 / 892)	9·3 (26 / 281)	12·4 (76 / 611)	0·479
Both	0·6 (5 / 892)	0·4 (1 / 281)	0·7 (4 / 611)	
Heart Failure	17·7 (158 / 894)	18·5 (52 / 281)	17·3 (106 / 613)	0·658
NYHA I	2·9 (26 / 891)	1·8 (5 / 281)	3·4 (21 / 610)	
NYHA II	5·2 (46 / 891)	7·5 (21 / 281)	4·1 (25 / 610)	0·183
NYHA III	8·1 (72 / 891)	8·2 (23 / 281)	8·0 (49 / 610)	
NYHA IV	1·2 (11 / 891)	1·1 (3 / 281)	1·3 (8 / 610)	
Chronic kidney failure	10·5 (94 / 897)	12·8 (36 / 281)	9·4 (58 / 616)	0·123
Conservative	8·2 (74 / 897)	10·7 (30 / 281)	7·1 (44 / 616)	0·203
Hemodialysis	2·1 (19 / 897)	2·1 (6 / 281)	2·1 (13 / 616)	
COPD	12·0 (107 / 888)	17·9 (50 / 280)	9·4 (57 / 608)	0·0003
Systemic steroids	0·7 (6 / 839)	1·6 (4 / 258)	0·3 (2 / 581)	
Inhaled steroids	5·5 (46 / 839)	8·5 (22 / 258)	4·1 (24 / 581)	0·014
Both	0·7 (6 / 839)	0·8 (2 / 258)	0·7 (4 / 581)	
Cancer	24·4 (219 / 896)	16·0 (45 / 181)	28·3 (174 / 615)	< 0·0001
Lung	0·8 (7 / 892)	0·7 (2 / 280)	0·8 (5 / 612)	
Prostate	1·6 (14 / 892)	1·4 (4 / 280)	1·6 (10 / 612)	
Brain	1·3 (12 / 892)	0·4 (1 / 280)	1·8 (11 / 612)	
Liver	1·2 (11 / 892)	0·0 (0 / 280)	1·8 (11 / 612)	
Kidney	0·6 (5 / 892)	0·4 (1 / 280)	0·7 (4 / 612)	
Stomach	1·8 (16 / 892)	1·1 (3 / 280)	2·1 (13 / 612)	
Pancreas	1·3 (12 / 892)	0·7 (2 / 280)	1·6 (10 / 612)	
Hematologic	2·2 (20 / 892)	1·4 (4 / 280)	2·6 (16 / 612)	
Breast	1·2 (11 / 892)	1·4 (4 / 280)	1·1 (7 / 612)	0·090
Colorectal	3·7 (33 / 892)	2·5 (7 / 280)	4·2 (26 / 612)	
Esophagus	1·2 (11 / 892)	0·7 (2 / 280)	1·5 (9 / 612)	
Head and Neck	1·7 (15 / 892)	0·7 (2 / 280)	2·1 (13 / 612)	
Uterus / Ovarian / Endometrium	1·8 (16 / 892)	1·4 (4 / 280)	2·0 (12 / 612)	
Testicle	0·3 (3 / 892)	0·0 (0 / 280)	0·5 (3 / 612)	
Intestinal / Retroperiteoneum	1·2 (11 / 892)	0·4 (1 / 280)	1·6 (10 / 612)	
Bladder	0·7 (6 / 892)	0·7 (2 / 280)	0·7 (4 / 612)	
Other	1·2 (11 / 892)	1·4 (4 / 280)	1·1 (7 / 612)	
Neuromuscular disease	2·1 (19 / 895)	1·8 (5 / 281)	3·1 (19 / 614)	0·750
Guillain-Barre	0·1 (1 / 895)	0·0 (0 / 281)	0·2 (1 / 614)	
Multiple sclerosis	0·1 (1 / 895)	0·0 (0 / 281)	0·2 (1 / 614)	
Amyotrophic lateral sclerosis	0·0 (0 / 895)	0·0 (0 / 281)	0·0 (0 / 614)	0·750
Myasthenia	0·3 (3 / 895)	0·0 (0 / 281)	0·5 (3 / 614)	
Parkinson	0·6 (5 / 895)	0·4 (1 / 281)	0·7 (4 / 614)	
Other	1·6 (14 / 895)	1·4 (4 / 281)	1·6 (10 / 614)	
Immunosuppression	7·8 (70 / 895)	7·8 (22 / 281)	7·5 (46 / 612)	0·995
Chemotherapy	2·9 (26 / 893)	2·5 (7 / 281)	3·1 (19 / 612)	
Human immunodeficiency virus	1·0 (9 / 893)	1·1 (3 / 281)	1·0 (6 / 612)	0·957
Steroids	1·9 (17 / 893)	2·1 (6 / 281)	1·8 (11 / 612)	
Other	1·8 (16 / 893)	2·1 (6 / 281)	1·6 (10 / 612)	

ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Failure
Data presented as % (n / total)
*: patient can have more than one diagnosis
a: *p* value represents comparison between risk categories for each variable

eTable 5 – Use of adjunctive and other therapies in invasively ventilated critically ill patients by risk of ARDS

	All (*n* = 935)	At Risk (*n* = 282)	At No Risk (*n* = 653)	*p* value[a]
Use of rescue therapy[*]				
Any	1·9 (16 / 855)	3·8 (10 / 263)	1·2 (7 / 592)	0·005
Recruitment maneuvers	1·4 (12 / 855)	2·3 (6 / 263)	0·8 (6 / 592)	0·115
ECMO	0·2 (2 / 855)	0·8 (2 / 263)	0·0 (0 / 592)	0·118
Prone positioning	0·3 (3 / 855)	0·8 (2 / 263)	0·2 (1 / 592)	0·430
Inhaled nitric oxide	0·0 (0 / 855)	0·0 (0 / 263)	0·0 (0 / 592)	---
$ECCO_2R$	0·0 (0 / 855)	0·0 (0 / 263)	0·0 (0 / 592)	---
HFOV	0·0 (0 / 855)	0·0 (0 / 263)	0·0 (0 / 592)	---

ECMO: extracorporeal membrane oxygenation; $ECCO_2R$: extracorporeal removal of carbon dioxide; HFOV: high frequency oscillatory ventilation;

*: patient can use more than one maneuver

a: *p* value represents comparison between risk categories for each variable

eTable 6 – Analyses from the false discovery rate using the Benjamini-Hochberg procedure with a false discovery rate of 0·2

Variable	*p* value	Benjamini-Hochberg *p* value	Significant*
ICU LOS	0·0000000000	0·0000000019	Yes
ICU Mortality	0·0000000041	0·0000000389	Yes
Hospital LOS	0·0000000091	0·0000000576	Yes
Acute Kidney Injury	0·0000001859	0·0000008830	Yes
Hospital Mortality	0.0000004230	0·0000016074	Yes
90-Day Mortality	0·0000005896	0·0000018670	Yes
Pulmonary Complications	0·0003306110	0·0008973727	Yes
Tracheostomy	0·0013227841	0·0031416122	Yes
VFD-28	0·0015164855	0·0032014693	Yes
ARDS	0·0049296319	0·0093663006	Yes
Extra-Pulmonary Infection	0·0089340372	0·0154315188	Yes
Cardiogenic Pulmonary oedema	0·0166391968	0·0263453949	Yes
Pleural Effusion	0·0217565660	0·0317980580	Yes
Pneumonia	0·0296331806	0·0402164593	Yes
New Pulmonary Infiltrate	0·0561260639	0·0710930142	Yes
Renal Replacement Therapy	0·1297727285	0·1541051150	No
Duration of Ventilation	0·2033855444	0·2273132555	No
Atelectasis	0·5719028045	0·6036751825	No
Pneumothorax	0·7290929272	0·7290929272	No

ICU: intensive care unit; LOS: length of stay; VFD: ventilator-free days; ARDS: acute respiratory distress syndrome

*: significance according to the false discovery rate of 0·2

eTable 7 – Characteristics of critically ill patients treated with invasive ventilation by presence of ARDS

	Patients Without ARDS (*n* = 935)	Patients With ARDS (*n* = 86)	*p* value[a]
Severity of illness, SOFA score[b]			
SOFA	6·0 (4·0 – 9·0)	9·0 (7·0 – 13·0)	< 0·0001
Pulmonary	2·0 (0·0 – 3·0)	3·0 (3·0 – 4·0)	< 0·0001
Hematologic	0·0 (0·0 – 1·0)	0·0 (0·0 – 1·0)	0·108
Liver	0·0 (0·0 – 0·0)	0·0 (0·0 – 1·0)	0·156
Circulation	1·0 (0·0 – 3·0)	2·0 (0·0 – 4·0)	0·046
Neurology	2·0 (0·0 – 4·0)	3·0 (0·0 – 4·0)	0·054
Renal	0·0 (0·0 – 1·0)	1·0 (0·0 – 2·0)	0·0001
Ventilator settings			
Mode of ventilation			
Volume-controlled	13·7 (116 / 849)	14·8 (12 / 81)	
Pressure-controlled	22·7 (193 / 849)	34·6 (28 / 81)	
Pressure support	9·4 (80 / 849)	6·2 (5 / 81)	
SIMV	26·3 (223 / 849)	25·9 (21 / 81)	
BiPAP / APRV	21·8 (185 / 849)	9·9 (8 / 81)	0·030
ASV	2·0 (17 / 849)	1·2 (1 / 81)	
PAV	0·0 (0 / 849)	0·0 (0 / 81)	
NAVA	0·1 (1 / 849)	0·0 (0 / 81)	
VAPS	0·9 (8 / 849)	2·5 (2 / 81)	
PRVC	2·7 (23 / 849)	2·5 (2 / 81)	
Other	0·4 (3 / 849)	2·5 (2 / 81)	
Ventilatory parameters			
Peak pressure, cmH_2O	20·0 (17·0 – 24·0)	24·0 (20·0 – 28·0)	< 0·0001
Plateau pressure, cmH_2O[c]	16·0 (13·0 – 20·0)	19·0 (16·2 – 25·0)	< 0·0001
No of patients	36·7 (343 / 935)	41·9 (36 / 86)	0·401
Tidal volume, milliliters	500 (440 – 575)	479 (413 – 542)	0·045
Tidal volume, ml/kg PBW	7·9 (6·8 – 9·1)	7·7 (6·7 – 9·1)	0·573
Control vent mode	7·7 (6·7 – 8·9)	7·4 (6·5 – 9·1)	0·458
Spontaneous vent mode	8·0 (6·8 – 9·2)	8·0 (6·9 – 9·0)	0·823
p value (control vs spont mode)	0·089	0·417	
≤ 7	29·8 (242 / 811)	32·9 (25 / 76)	
7 – 8	42·8 (347 / 811)	39·5 (30 / 76)	0·546
9 – 10	19·9 (161 / 811)	23·7 (18 / 76)	
> 10	7·5 (61 / 811)	3·9 (3 / 76)	
PEEP, cmH_2O	5·0 (5·0 – 8·0)	8·0 (5·0 – 10·0)	< 0·0001
≤ 5	54·2 (450 / 830)	29·9 (23 / 77)	
6 – 8	30·5 (253 / 830)	33·8 (26 / 77)	< 0·0001
9 – 10	10·4 (86 / 830)	18·2 (14 / 77)	
> 10	4·9 (41 / 830)	18·2 (14 / 77)	
Driving pressure, cmH_2O	10·0 (6·0 – 13·0)	11·5 (8·0 – 15·7)	0·009
Respiratory rate, bpm	15·0 (12·0 – 18·0)	16·0 (14·0 – 20·0)	< 0·0001
FiO_2	0·5 (0·4 – 0·6)	0·6 (0·5 – 0·8)	< 0·0001
Static Compliance, ml/cmH_2O	54·2 (36·9 – 77·1)	43·7 (32·0 – 55·5)	0·006
Minute-Ventilation, l/min	7·4 (6·2 – 8·9)	7·7 (7·0 – 9·6)	0·034
Laboratory and clinical data			
Laboratory parameters			
PaO_2 / FiO_2, mmHg	261 (165 – 367)	141 (108 – 212)	< 0·0001
$PaCO_2$, mmHg	38·0 (34·0 – 45·0)	45·0 (37·0 – 52·5)	0·001
pH	7·36 (7·30 – 7·42)	7·34 (7·21 – 7·42)	0·003
HCO_3, mEq/liter	22·0 (20·0 – 25·0)	23·0 (18·7 – 28·0)	0·405
Use of adjunctive and other therapies			
Use of rescue therapy*	1·9 (16 / 855)	12·3 (10 / 81)	< 0·0001
Recruitment maneuvers	1·4 (12 / 855)	8·6 (7 / 81)	0·0001
ECMO	0·2 (2 / 855)	0·0 (0 / 81)	0·337
Prone positioning	0·3 (3 / 855)	4·9 (4 / 81)	0·0001
Inhaled nitric oxide	0·0 (0 / 855)	0·0 (0 / 81)	---
$ECCO_2R$	0·0 (0 / 855)	0·0 (0 / 81)	---
HFOV	0·0 (0 / 855)	0·0 (0 / 81)	---

ARDS: acute respiratory distress syndrome; LIPS: Lung Injury Prediction Score; SOFA: Sequential Organ Failure Assessment; SIMV: synchronized intermittent mandatory ventilation; BiPAP: biphasic positive airway pressure; APRV: airway pressure release ventilation; ASV: adaptive support ventilation; PAV: proportional assist ventilation; NAVA: neurally adjusted ventilatory assist; VAPS: volume-assured pressure support; PRVC: pressure regulated volume control; PEEP: positive end-expiratory pressure, FiO_2: inspired fraction of oxygen; PaO_2: partial pressure of oxygen; $PaCO_2$: partial pressure of carbon dioxide; HCO_3: bicarbonate; SpO_2: pulse oximetry; $etCO_2$: end tidal fraction of carbon dioxide; ECMO: extracorporeal membrane oxygenation; $ECCO_2R$: extracorporeal removal of carbon dioxide; HFOV: high frequency oscillatory ventilation; RASS: Richmond Agitation Sedation Scale; PBW: predicted body weight; MAP: mean arterial blood pressure; BPM: beats per minute

*: patient can use more than one maneuver

a: *p* value represents comparison between presence or absence of ARDS

b: for all SOFA scores for which data points were missing, this value was omitted and the denominator adjusted accordingly
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	All (*n* = 935)	At Risk (*n* = 282)	At No Risk (*n* = 653)	*p* value[a]
Use of rescue therapy[*]				
Any	1·9 (16 / 855)	3·8 (10 / 263)	1·2 (7 / 592)	0·005
Recruitment maneuvers	1·4 (12 / 855)	2·3 (6 / 263)	0·8 (6 / 592)	0·115
ECMO	0·2 (2 / 855)	0·8 (2 / 263)	0·0 (0 / 592)	0·118
Prone positioning	0·3 (3 / 855)	0·8 (2 / 263)	0·2 (1 / 592)	0·430
Inhaled nitric oxide	0·0 (0 / 855)	0·0 (0 / 263)	0·0 (0 / 592)	---
$ECCO_2R$	0·0 (0 / 855)	0·0 (0 / 263)	0·0 (0 / 592)	---
HFOV	0·0 (0 / 855)	0·0 (0 / 263)	0·0 (0 / 592)	---

ECMO: extracorporeal membrane oxygenation; $ECCO_2R$: extracorporeal removal of carbon dioxide; HFOV: high frequency oscillatory ventilation;

*: patient can use more than one maneuver

a: *p* value represents comparison between risk categories for each variable

eTable 6 – Analyses from the false discovery rate using the Benjamini-Hochberg procedure with a false discovery rate of 0·2

Variable	*p* value	Benjamini-Hochberg *p* value	Significant*
ICU LOS	0·0000000000	0·0000000019	Yes
ICU Mortality	0·0000000041	0·0000000389	Yes
Hospital LOS	0·0000000091	0·0000000576	Yes
Acute Kidney Injury	0·0000001859	0·0000008830	Yes
Hospital Mortality	0.0000004230	0·0000016074	Yes
90-Day Mortality	0·0000005896	0·0000018670	Yes
Pulmonary Complications	0·0003306110	0·0008973727	Yes
Tracheostomy	0·0013227841	0·0031416122	Yes
VFD-28	0·0015164855	0·0032014693	Yes
ARDS	0·0049296319	0·0093663006	Yes
Extra-Pulmonary Infection	0·0089340372	0·0154315188	Yes
Cardiogenic Pulmonary oedema	0·0166391968	0·0263453949	Yes
Pleural Effusion	0·0217565660	0·0317980580	Yes
Pneumonia	0·0296331806	0·0402164593	Yes
New Pulmonary Infiltrate	0·0561260639	0·0710930142	Yes
Renal Replacement Therapy	0·1297727285	0·1541051150	No
Duration of Ventilation	0·2033855444	0·2273132555	No
Atelectasis	0·5719028045	0·6036751825	No
Pneumothorax	0·7290929272	0·7290929272	No

ICU: intensive care unit; LOS: length of stay; VFD: ventilator-free days; ARDS: acute respiratory distress syndrome

*: significance according to the false discovery rate of 0·2

eTable 7 – Characteristics of critically ill patients treated with invasive ventilation by presence of ARDS

	Patients Without ARDS (*n* = 935)	Patients With ARDS (*n* = 86)	*p* value[a]
Severity of illness, SOFA score[b]			
SOFA	6·0 (4·0 – 9·0)	9·0 (7·0 – 13·0)	< 0·0001
Pulmonary	2·0 (0·0 – 3·0)	3·0 (3·0 – 4·0)	< 0·0001
Hematologic	0·0 (0·0 – 1·0)	0·0 (0·0 – 1·0)	0·108
Liver	0·0 (0·0 – 0·0)	0·0 (0·0 – 1·0)	0·156
Circulation	1·0 (0·0 – 3·0)	2·0 (0·0 – 4·0)	0·046
Neurology	2·0 (0·0 – 4·0)	3·0 (0·0 – 4·0)	0·054
Renal	0·0 (0·0 – 1·0)	1·0 (0·0 – 2·0)	0·0001
Ventilator settings			
Mode of ventilation			
Volume-controlled	13·7 (116 / 849)	14·8 (12 / 81)	
Pressure-controlled	22·7 (193 / 849)	34·6 (28 / 81)	
Pressure support	9·4 (80 / 849)	6·2 (5 / 81)	
SIMV	26·3 (223 / 849)	25·9 (21 / 81)	
BiPAP / APRV	21·8 (185 / 849)	9·9 (8 / 81)	0·030
ASV	2·0 (17 / 849)	1·2 (1 / 81)	
PAV	0·0 (0 / 849)	0·0 (0 / 81)	
NAVA	0·1 (1 / 849)	0·0 (0 / 81)	
VAPS	0·9 (8 / 849)	2·5 (2 / 81)	
PRVC	2·7 (23 / 849)	2·5 (2 / 81)	
Other	0·4 (3 / 849)	2·5 (2 / 81)	
Ventilatory parameters			
Peak pressure, cmH_2O	20·0 (17·0 – 24·0)	24·0 (20·0 – 28·0)	< 0·0001
Plateau pressure, cmH_2O[c]	16·0 (13·0 – 20·0)	19·0 (16·2 – 25·0)	< 0·0001
No of patients	36·7 (343 / 935)	41·9 (36 / 86)	0·401
Tidal volume, milliliters	500 (440 – 575)	479 (413 – 542)	0·045
Tidal volume, ml/kg PBW	7·9 (6·8 – 9·1)	7·7 (6·7 – 9·1)	0·573
Control vent mode	7·7 (6·7 – 8·9)	7·4 (6·5 – 9·1)	0·458
Spontaneous vent mode	8·0 (6·8 – 9·2)	8·0 (6·9 – 9·0)	0·823
p value (control vs spont mode)	0·089	0·417	
≤ 7	29·8 (242 / 811)	32·9 (25 / 76)	
7 – 8	42·8 (347 / 811)	39·5 (30 / 76)	0·546
9 – 10	19·9 (161 / 811)	23·7 (18 / 76)	
> 10	7·5 (61 / 811)	3·9 (3 / 76)	
PEEP, cmH_2O	5·0 (5·0 – 8·0)	8·0 (5·0 – 10·0)	< 0·0001
≤ 5	54·2 (450 / 830)	29·9 (23 / 77)	
6 – 8	30·5 (253 / 830)	33·8 (26 / 77)	< 0·0001
9 – 10	10·4 (86 / 830)	18·2 (14 / 77)	
> 10	4·9 (41 / 830)	18·2 (14 / 77)	
Driving pressure, cmH_2O	10·0 (6·0 – 13·0)	11·5 (8·0 – 15·7)	0·009
Respiratory rate, bpm	15·0 (12·0 – 18·0)	16·0 (14·0 – 20·0)	< 0·0001
FiO_2	0·5 (0·4 – 0·6)	0·6 (0·5 – 0·8)	< 0·0001
Static Compliance, ml/cmH_2O	54·2 (36·9 – 77·1)	43·7 (32·0 – 55·5)	0·006
Minute-Ventilation, l/min	7·4 (6·2 – 8·9)	7·7 (7·0 – 9·6)	0·034
Laboratory and clinical data			
Laboratory parameters			
PaO_2 / FiO_2, mmHg	261 (165 – 367)	141 (108 – 212)	< 0·0001
$PaCO_2$, mmHg	38·0 (34·0 – 45·0)	45·0 (37·0 – 52·5)	0·001
pH	7·36 (7·30 – 7·42)	7·34 (7·21 – 7·42)	0·003
HCO_3, mEq/liter	22·0 (20·0 – 25·0)	23·0 (18·7 – 28·0)	0·405
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Recruitment maneuvers	1·4 (12 / 855)	8·6 (7 / 81)	0·0001
ECMO	0·2 (2 / 855)	0·0 (0 / 81)	0·337
Prone positioning	0·3 (3 / 855)	4·9 (4 / 81)	0·0001
Inhaled nitric oxide	0·0 (0 / 855)	0·0 (0 / 81)	---
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ARDS: acute respiratory distress syndrome; LIPS: Lung Injury Prediction Score; SOFA: Sequential Organ Failure Assessment; SIMV: synchronized intermittent mandatory ventilation; BiPAP: biphasic positive airway pressure; APRV: airway pressure release ventilation; ASV: adaptive support ventilation; PAV: proportional assist ventilation; NAVA: neurally adjusted ventilatory assist; VAPS: volume-assured pressure support; PRVC: pressure regulated volume control; PEEP: positive end-expiratory pressure, FiO_2: inspired fraction of oxygen; PaO_2: partial pressure of oxygen; $PaCO_2$: partial pressure of carbon dioxide; HCO_3: bicarbonate; SpO_2: pulse oximetry; $etCO_2$: end tidal fraction of carbon dioxide; ECMO: extracorporeal membrane oxygenation; $ECCO_2R$: extracorporeal removal of carbon dioxide; HFOV: high frequency oscillatory ventilation; RASS: Richmond Agitation Sedation Scale; PBW: predicted body weight; MAP: mean arterial blood pressure; BPM: beats per minute

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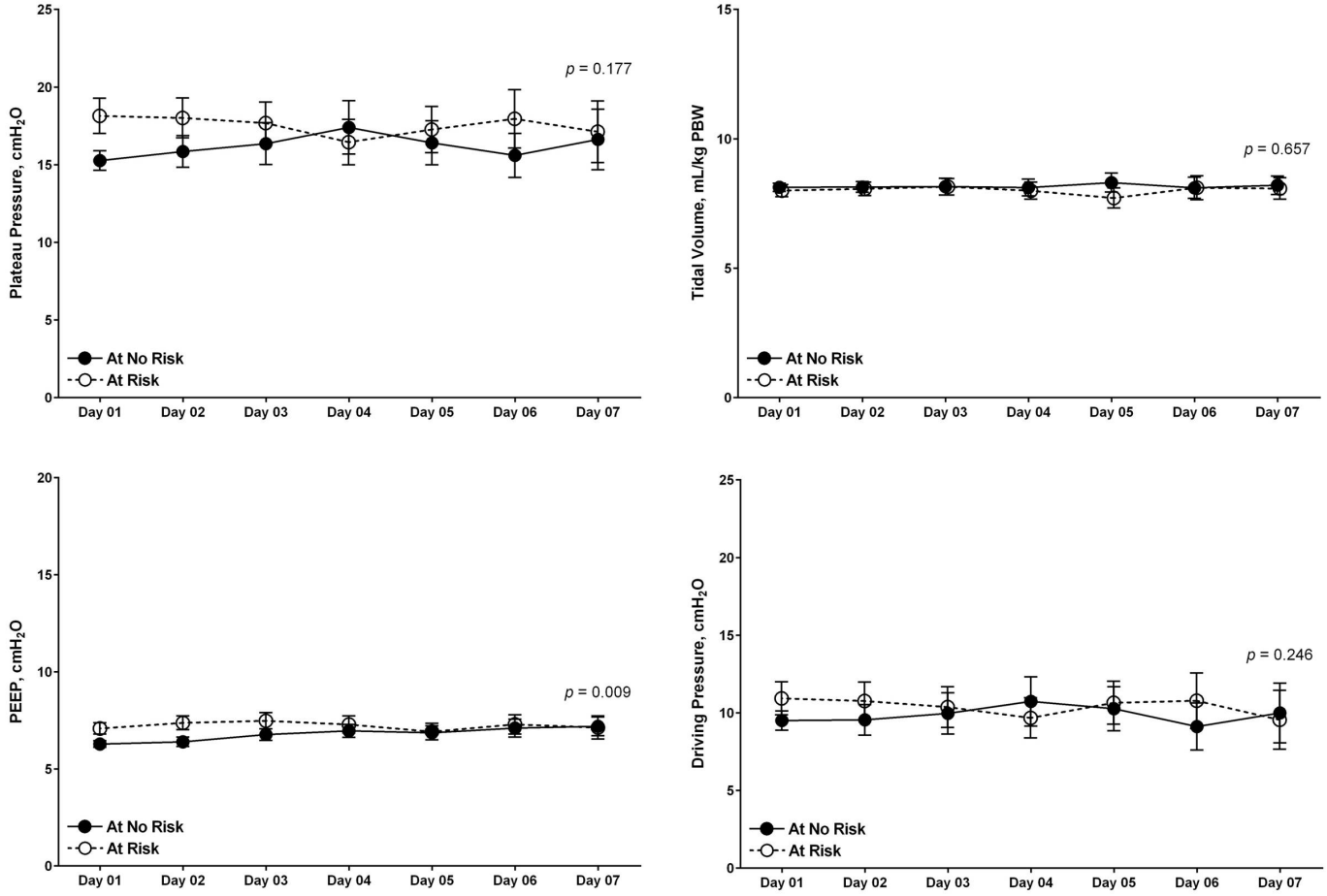
eTable 8 – LIPS performance at different cut-off points

	≥ 4	**> 5**	**> 6**	**> 7**	**> 8**
Prevalence of ARDS (95% CI)	7·8 (4·8 - 10·8)	11·0 (6·9 - 15·2)	17·0 (10·8 - 23·2)	26·7 (17·5 - 35·8)	30·6 (19·2 - 42·1)
Sensitivity (95% CI)	0·67 (0·49 – 0·81)	0·39 (0·23 – 0·56)	0·25 (0·12 – 0·42)	0·14 (0·05 – 0·29)	0·11 (0·03 – 0·26)
Specificity (95% CI)	0·63 (0·59 – 0·66)	0·73 (0·70 – 0·76)	0·83 (0·80 – 0·85)	0·89 (0·86 – 0·91)	0·92 (0·90 – 0·94)
+ Likelihood Ratio (95% CI)	1·8 (1·4 – 2·3)	1·4 (0·9 – 2·2)	1·4 (0·8 – 2·6)	1·2 (0·5 – 2·9)	1·5 (0·6 – 3·8)
- Likelihood Ratio (95% CI)	0·5 (0·3 – 0·8)	0·8 (0·6 – 1·1)	0·9 (0·8 – 1·1)	0·9 (0·8 – 1·1)	0·9 (0·9 – 1·1)

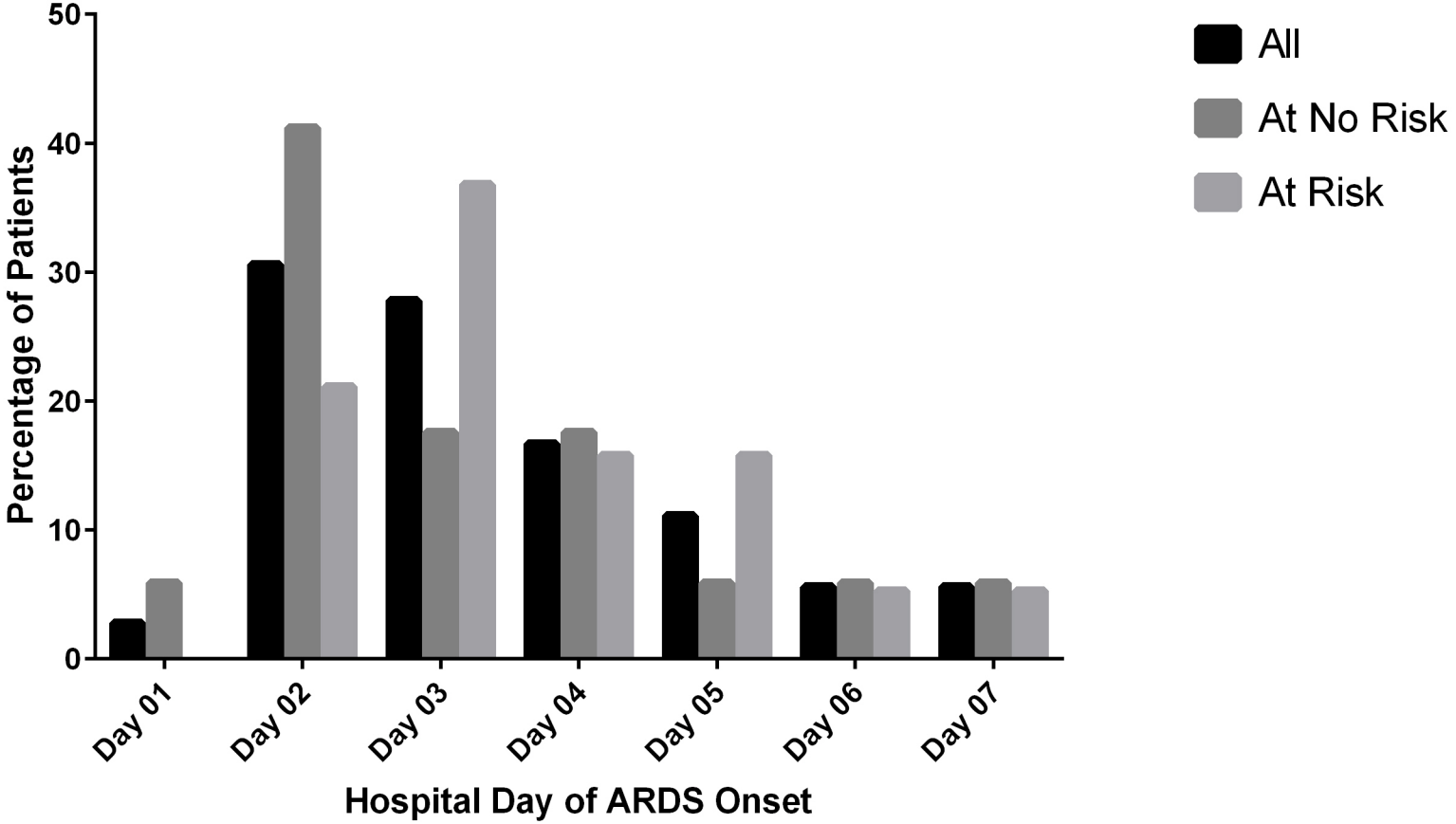
LIPS: Lung Injury Prediction Score; ARDS: acute respiratory distress syndrome; CI: confidence interval

eFigure 1 – Ventilatory parameters in the first seven days of ventilation in patients at risk and at no risk of ARDS

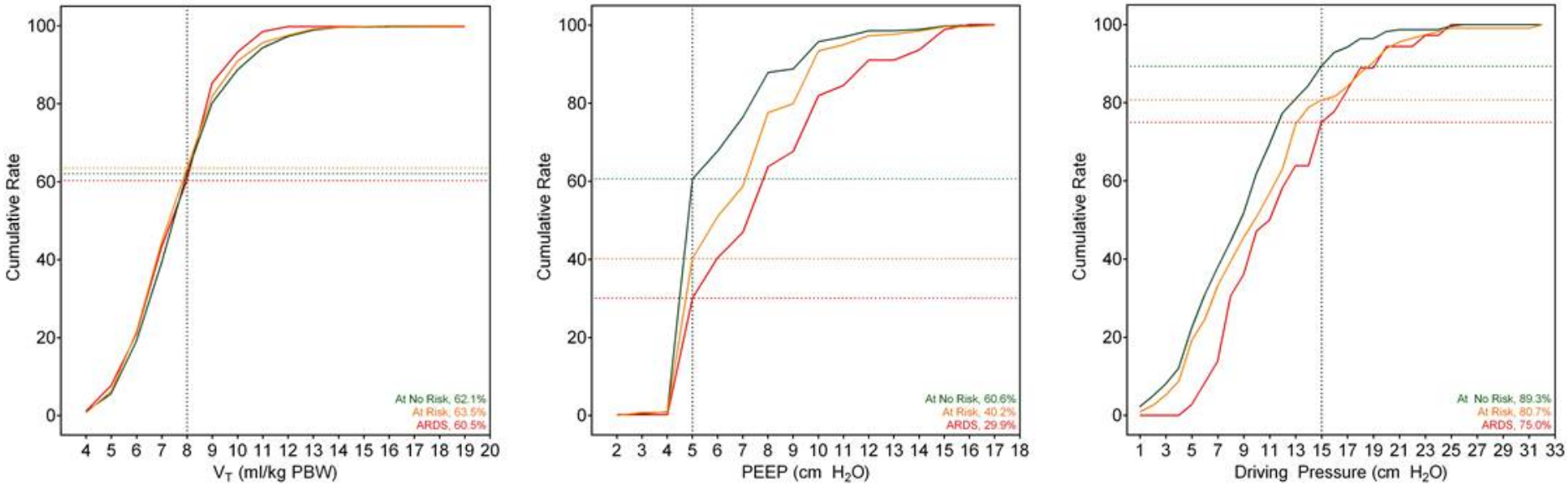


Lines are means and bars 95% confidence interval. PEEP is positive end-expiratory pressure and PBW is predicted body weight. *p* value is for time-group interaction

eFigure 2 – Timing of ARDS development during hospital stay



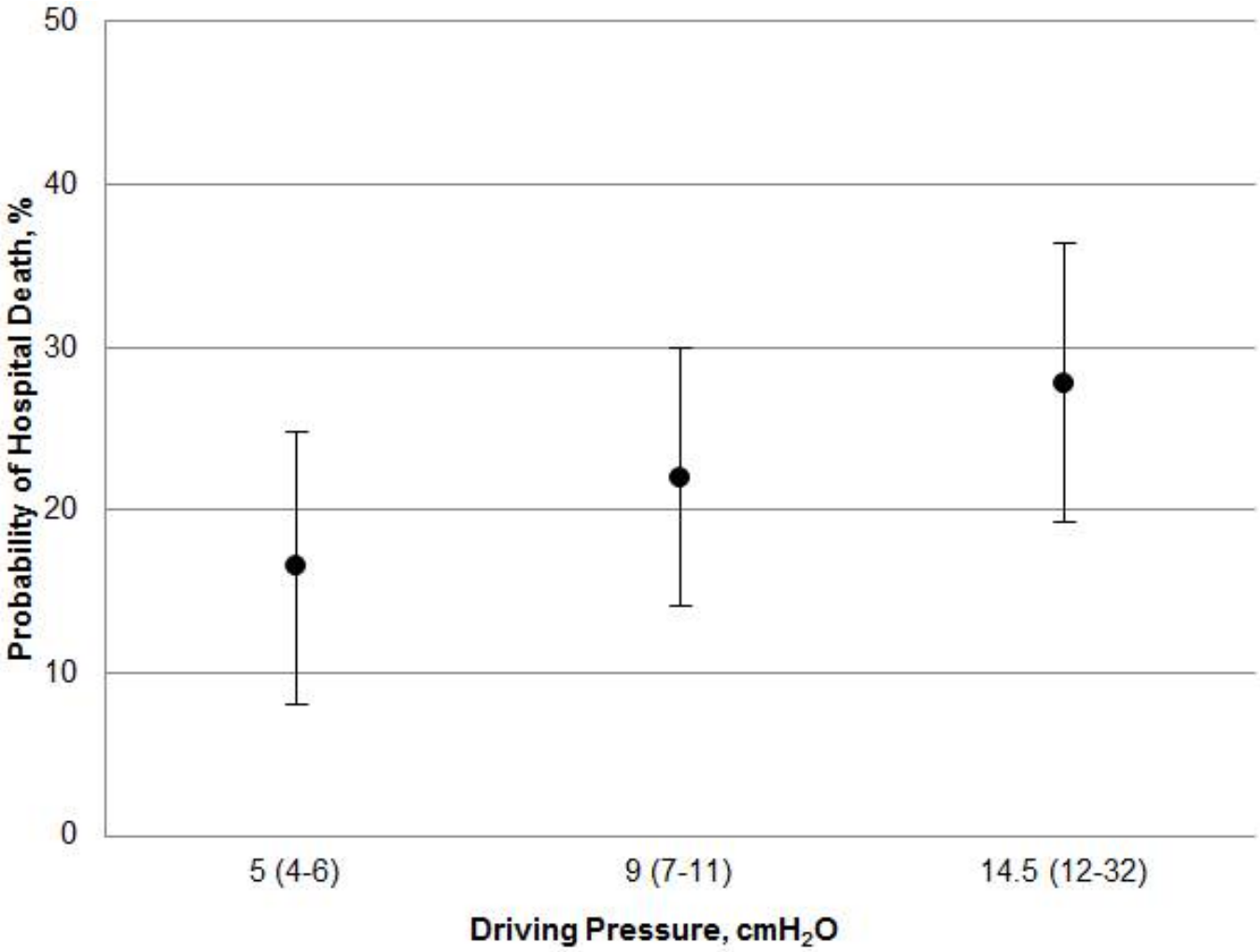
eFigure 3 – Ventilation parameters in patients at risk of ARDS and with ARDS



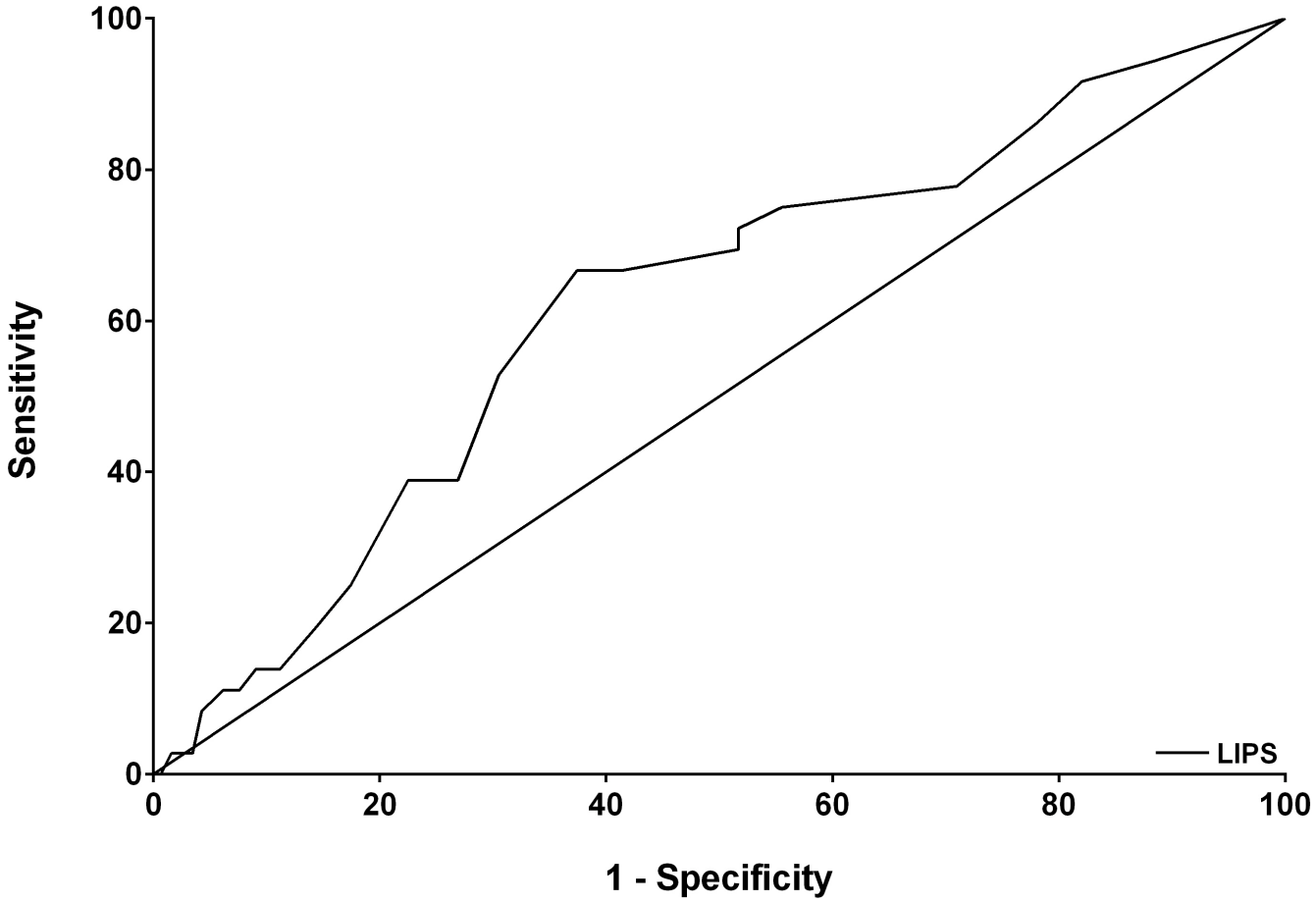
Cumulative frequency distribution of tidal volume (A); cumulative frequency distribution of positive end–expiratory pressure (B); and cumulative distribution of driving pressure (C)

Abbreviations: PBW: predicted body weight; V_T: tidal volume

eFigure 4 – Driving pressure tertiles and outcome



eFigure 5 – ROC curve for LIPS in the cohort of the preset study



Outcome variable was development of ARDS. LIPS is Lung Injury Prediction Score