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# Prognostic classification based on P/F and PEEP in invasively ventilated ICU patients with hypoxemia—insights from the MARS study

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## Abstract

**Background:** Outcome prediction in patients with acute respiratory distress syndrome (ARDS) greatly improves when patients are reclassified based on predefined arterial oxygen partial pressure to fractional inspired oxygen ratios ( $\text{PaO}_2/\text{FiO}_2$ ) and positive end-expiratory pressure (PEEP) cutoffs 24 h after the initial ARDS diagnosis. The aim of this study was to test whether outcome prediction improves when patients are reclassified based on predefined  $\text{PaO}_2/\text{FiO}_2$  and PEEP cutoffs 24 h after development of mild hypoxemia while not having ARDS.

**Methods:** Post hoc analysis of a large prospective, multicenter, observational study that ran in the ICUs of two academic hospitals in the Netherlands between January 2011 and December 2013. Patients were classified into four groups using predefined cutoffs for  $\text{PaO}_2/\text{FiO}_2$  (250 mmHg) and PEEP (5 cm  $\text{H}_2\text{O}$ ), both at onset of hypoxemia and after 24 h:  $\text{PaO}_2/\text{FiO}_2 \geq 250$  mmHg and  $\text{PEEP} < 6$  cm  $\text{H}_2\text{O}$  (group I),  $\text{PaO}_2/\text{FiO}_2 \geq 250$  mmHg and  $\text{PEEP} \geq 6$  cm  $\text{H}_2\text{O}$  (group II),  $\text{PaO}_2/\text{FiO}_2 < 250$  mmHg and  $\text{PEEP} < 6$  cm  $\text{H}_2\text{O}$  (group III), and  $\text{PaO}_2/\text{FiO}_2 < 250$  mmHg and  $\text{PEEP} \geq 6$  cm  $\text{H}_2\text{O}$  (group IV), to look for trend association with all-cause in-hospital mortality, the primary outcome. Secondary outcome were ICU- and 90-day mortality, and the number of ventilator-free days or ICU-free days and alive at day 28.

**Results:** The analysis included 689 consecutive patients. All-cause in-hospital mortality was 35%. There was minimal variation in mortality between the four groups at onset of hypoxemia (33, 36, 38, and 34% in groups I to IV, respectively;  $P = 0.65$ ). Reclassification after 24 h resulted in a strong trend with increasing mortality from group I to group IV (31, 31, 37, and 48% in groups I to IV, respectively;  $P < 0.01$ ). Similar trends were found for the secondary endpoints.

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**Conclusions:** Reclassification using  $\text{PaO}_2/\text{FiO}_2$  and PEEP cutoffs after 24 h improved classification for outcome in invasively ventilated ICU patients with hypoxemia not explained by ARDS, compared to classification at onset of hypoxemia.

**Trial registration:** [ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT01905033. Registered on July 11, 2013. Retrospectively registered.

**Keywords:** Intensive care unit, Invasive ventilation, Hypoxemia, Prognostication, Mortality, Ventilator-free days, ICU-free days, P/F,  $\text{PaO}_2/\text{FiO}_2$ , Positive end-expiratory pressure, PEEP

## Background

Hypoxemia commonly develops in invasively ventilated intensive care unit (ICU) patients. While hypoxemia could reflect the presence of pulmonary injury, including acute respiratory distress syndrome (ARDS) [1], it is more likely to be caused by positive pressure ventilation-induced effects on pulmonary circulation [2, 3] or atelectases [4, 5].

Two investigations showed that outcome prediction in adult patients with ARDS greatly improves when patients are reclassified based on predefined arterial oxygen partial pressure to fractional inspired oxygen ratios ( $\text{PaO}_2/\text{FiO}_2$ ) and positive end-expiratory pressures (PEEP) cutoffs 24 h after the initial ARDS diagnosis [6, 7]. Similar results came from a study in children with ARDS [8]. These findings, at least in part are in line with the recent finding that patients with “resolved” ARDS, i.e., patients who no longer meet the criteria for ARDS after 24 h have a much lower mortality than those with “confirmed” ARDS, i.e., those patients who remain to fulfil these criteria [9].

Whether reclassification based on  $\text{PaO}_2/\text{FiO}_2$  and PEEP cutoffs is also helpful in identifying subsets of ICU patients who develop hypoxemia after start of invasive ventilation is uncertain. The present study, therefore, tested the hypothesis that reclassification after 24 h based on predefined  $\text{PaO}_2/\text{FiO}_2$  and PEEP cutoffs improves outcome prediction in invasively ventilated ICU patients with mild hypoxemia from another cause than ARDS. For this analysis, the database of the conveniently sized prospective “Molecular Diagnosis and Risk Stratification of Sepsis” (MARS) study was used [10].

## Methods

### Design

This was a post hoc analysis of the database of the MARS study that included patients admitted to the mixed medical–surgical ICUs of two university hospitals in the Netherlands: the Amsterdam University Medical Centers (AUMC), location Academic Medical Center, Amsterdam, The Netherlands, and the University Medical Center Utrecht (UMCU), Utrecht, The Netherlands.

Inclusion in the MARS study was with an opt-out consent method approved by the Institutional Review Board of the UMCU with ID no. 10-056C on June 16, 2010. The MARS study was registered at [clinicaltrials.gov](https://clinicaltrials.gov) with study identifier NCT01905033.

### Patients

Consecutive adult patients with an anticipated length of stay in ICU of more than 24 h and admitted between January 2011 and December 2013 were eligible for the parent

study. Patients were eligible for participation in this post hoc analysis if they (a) developed hypoxemia, defined as having  $\text{PaO}_2/\text{FiO}_2 \geq 200$  and  $< 300$  mmHg at a minimum PEEP of 5 cm  $\text{H}_2\text{O}$ , within the first 24 h of invasive ventilation and (b) receiving invasive ventilation for at least 24 h. Patients were excluded if (a) meeting criteria for ARDS, (b) not having  $\text{PaO}_2/\text{FiO}_2$  after 24 h, hampering reclassification, or (c) when lost to follow up.

#### Data collection and definitions

Baseline and demographic variables were collected on ICU admission to calculate disease severity scores.  $\text{PaO}_2/\text{FiO}_2$  and PEEP at onset of hypoxemia and after 24 h were used for classification and reclassification of patients (see below).

Data collectors were trained in capturing reliable and stable data, thus considering only blood gas analysis results,  $\text{FiO}_2$  and PEEP when a patient was deemed clinically stable, as such ignoring temporary hypoxemic events that were related to accidental patient-ventilator disconnections, obstruction of endotracheal tubes by secretions, airway suctioning, or hemodynamic instability.

Data collectors of MARS were also trained in diagnosing ARDS by using the Berlin definition for ARDS [11].

#### Cutoffs for $\text{PaO}_2/\text{FiO}_2$ and PEEP

Patients were classified into four groups, based on pragmatic cutoffs for  $\text{PaO}_2/\text{FiO}_2$  and PEEP. Using these predefined cutoffs, patients could be classified into four groups:  $\text{PaO}_2/\text{FiO}_2 \geq 250$  mmHg and PEEP  $< 6$  cm  $\text{H}_2\text{O}$  (group I),  $\text{PaO}_2/\text{FiO}_2 \geq 250$  mmHg and PEEP  $\geq 6$  cm  $\text{H}_2\text{O}$  (group II),  $\text{PaO}_2/\text{FiO}_2 < 250$  mmHg and PEEP  $< 6$  cm  $\text{H}_2\text{O}$  (group III), and  $\text{PaO}_2/\text{FiO}_2 < 250$  mmHg and PEEP  $\geq 6$  cm  $\text{H}_2\text{O}$  (group IV). These cutoffs were chosen before data extraction and thus before start of the analysis, and were based on the most commonly used setting for PEEP in patient without ARDS [12]. For the  $\text{PaO}_2/\text{FiO}_2$ , we made a pragmatic choice for the middle of the range between 200 and 300.

#### Endpoints

The primary endpoint was all-cause in-hospital mortality. Secondary endpoints were ICU- and 90-day mortality, the number of ventilator-free days and alive at day 28, defined as the number of days a patient was alive and not ventilated until day 28 after admittance, and the number of ICU-free days and alive at day 28, defined as the number of days a patient was alive and not in the ICU until day 28 after admittance.

#### Standard care

Patients received invasive ventilation according to the local guidelines that prescribed the use of lung-protective settings aiming at tidal volumes  $< 8$  ml/kg predicted body-weight. PEEP and  $\text{FiO}_2$  uptitrations followed a strict protocol in which recruitment maneuvers were to be performed with every rise in PEEP with hypoxemia, and PEEP and  $\text{FiO}_2$  downtitrations with hyperoxemia.  $\text{PaO}_2$  and  $\text{SpO}_2$  targets were 8 to 10 kPa and 92 to 97%, respectively. Patients in controlled modes of ventilation were assessed at least three times per day to determine whether weaning could start, consisting of a switch to

pressure support ventilation. If pressure support ventilation was accepted well, this mode was to be used for further mechanical ventilatory support. Extubation was performed at the discretion of attending physicians, based on general extubation criteria (i.e., the patient was responsive and cooperative, had an adequate oxygenation with a maximum  $\text{FiO}_2$  of 0.4, was hemodynamically stable at low doses inotropes and without uncontrolled arrhythmia, and having a normal temperature) [13]. A restrictive fluid balance, targeting normovolemia, was used with a preference for crystalloid over colloid infusions. In case of shock, the SSC guidelines applicable at the time were followed [14]. Sedation scales were used for analgesation with bolus medication in all patients.

### Statistical analysis

Data were expressed as number or percentages, mean  $\pm$  standard deviation (SD), or median and interquartile range (IQR) where appropriate. Differences between distributions of categorical variables were analyzed with Pearson chi-square test and with *t* test or Kruskal–Wallis test for numerical variables.

As a first step, trend associations with outcome in the four classification groups based on the predefined  $\text{PaO}_2/\text{FiO}_2$  and PEEP cutoffs at onset of hypoxemia were determined. For the second step, patients were reclassified using the same cutoffs, but after 24 h. *P* values for linear trend for dichotomous outcome variables, i.e., all-cause in-hospital-, ICU-, and 90-day mortality, and *P* values for linear regression for continuous outcome variables, i.e., ventilator-free and ICU-free days and alive at day 28, were calculated for the classification groups, with the groups as the independent variable.

In one post hoc analysis, we compared the four groups for the primary outcome. A pairwise comparison was used at onset of hypoxemia and after 24 h, using a contrast matrix predictor approach. For each mutual comparison between groups, odds ratios and 95% confidence intervals were calculated.

A *P* value of  $< 0.05$  was considered statistically significant. All statistical analyses were conducted with R statistics (v.3.2.2) via the R-studio interface.

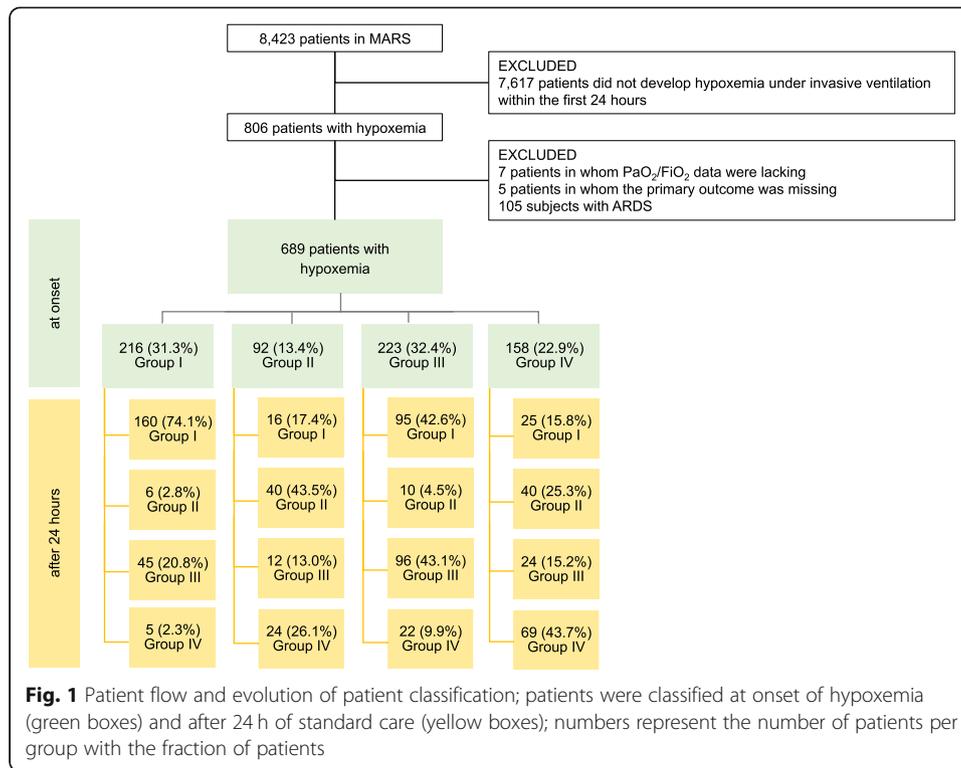
## Results

### Patients

Of 8423 admitted patients in the parent MARS study, 806 patients developed hypoxemia after start of invasive ventilation (Fig. 1). After exclusion of patients who met criteria for ARDS and patients with missing data, 689 patients were left for the current analysis. There were no patients who developed ARDS during follow-up. Overall, all-cause in-hospital mortality was 35% (242/689).

### Evolution of hypoxemia over 24 h

Hypoxemia severity varied significantly from onset till 24 h later (Fig. 1). For instance, of 216 patients in group I at onset of hypoxemia, 56 patients (26%) worsened over the next 24 h. Of 92 in group II, 36 patients (39%) worsened. Vice versa, of 223 and 158 patients in group III and IV, 105 patients (47%) and 65 patients (41%) improved.



### Hospital survivors versus non-survivors

Table 1 shows demographics and ventilation characteristics of hospital survivors versus non-survivors. Patients who died in the hospital were older and had higher APACHE IV scores, while patients who survived were more frequently admitted after elective surgery but less frequent after emergency surgery.  $\text{PaO}_2/\text{FiO}_2$ ,  $\text{PaO}_2$ , and PEEP at onset of hypoxemia were not different between hospital survivors and non-survivors, but became different between survivor and non-survivors at 24 h after onset of hypoxemia.

### Groups based on the predefined $\text{PaO}_2/\text{FiO}_2$ and PEEP cutoffs

Demographics and ventilation characteristics of the classification groups based on the predefined  $\text{PaO}_2/\text{FiO}_2$  and PEEP cutoffs at onset of hypoxemia and after 24 h are shown in Table 2. From group I to group IV,  $\text{FiO}_2$  and  $\text{PaCO}_2$  increased; APACHE IV also increased from group I to group IV, but this difference did not reach statistical significance.

### Risk of death in the classification groups

The pairwise comparison showed that in-hospital mortality was not significantly different between groups at onset of hypoxemia. Pairwise comparison after 24 h, however, showed a difference in all-cause in-hospital mortality between groups I and IV (OR, 0.48 [95% confidence interval, 0.26–0.86];  $P$  value for trend < 0.01) (Table 3). Other differences between groups did not reach statistical significance.

**Table 1** Baseline characteristics of patients with mild hypoxemia who survived and patients who died in the hospital

Characteristics	Survivors, <i>n</i> = 447	Non-survivors, <i>n</i> = 242	<i>P</i> value
APACHE IV score, median [IQR]	71 [56–87]	96 [76–116]	< 0.01
Age, median [IQR]	60 [49–69]	66 [57–75]	< 0.01
Gender, male, <i>n</i> (%)	281 (63)	160 (66)	0.40
Admission type, <i>n</i> (%)			
Medical	278 (62)	146 (60)	
Elective surgery	63 (14)	22 (9)	0.04
Emergency surgery	106 (24)	74 (31)	
Primary admission specialty, <i>n</i> (%)			
Cardiology	67 (15)	34 (14)	
Cardiothoracic surgery	78 (17)	28 (12)	
Ear, nose, and throat	7 (2)	3 (1)	
Gastro-oncologic surgery	7 (2)	5 (2)	
Gastroenterology	7 (2)	4 (8)	
General surgery	83 (19)	42 (17)	
Gynecology and obstetrics	3 (1)	0 (0)	0.03
Hematology	3 (1)	3 (1)	
Head and neck surgery	5 (1)	0 (0)	
Internal medicine	38 (8.5)	13 (5)	
Neurology	64 (14)	57 (24)	
Neurosurgery	45 (10)	35 (14.5)	
Orthopedic surgery	5 (1)	2 (1)	
Pulmonology	28 (6)	11 (4.5)	
Other	2 (0)	4 (2)	
Comorbidities, <i>n</i> (%)			
Diabetes mellitus	74 (17)	62 (26)	< 0.01
Immune deficiency	40 (9)	28 (12)	0.30
Cardiovascular disease	143 (32)	76 (31)	0.93
Any malignancy	58 (13)	39 (16)	0.28
COPD	59 (13)	38 (16)	0.43
<b>Ventilation and other parameters at onset of hypoxemia, median [IQR]</b>			
Maximum airway pressure, cm H <sub>2</sub> O	19 [16–23]	20 [17–24]	< 0.01
PEEP, cm H <sub>2</sub> O	5 [5–8]	5 [5–8]	0.94
FIO <sub>2</sub> , %	40 [40–41]	40 [40–41]	0.18
PaO <sub>2</sub> /FIO <sub>2</sub> , mmHg	245 [222–270]	241 [220–273]	0.99
Tidal volume, ml/kg PBW	7.2 [6.2–8.4]	6.9 [6–8.1]	0.19
Respiratory rate, per minute	18 [15–22]	19 [15–24]	0.01
PaO <sub>2</sub> , mmHg	110 [95–129]	105 [93–133]	0.30
PaCO <sub>2</sub> , mmHg	40 [36–46]	38 [34–43]	< 0.01
Dead space fraction	0.1 [0–0.2]	0.1 [0–0.2]	0.07
Use of vasopressors	252 (56)	165 (68)	< 0.01
<b>Ventilation and other parameters after 24 h, median [IQR]</b>			
Maximum airway pressure, cm H <sub>2</sub> O	17 [14–21]	18 [15–23]	0.01
PEEP, cm H <sub>2</sub> O	5 [5–6]	5 [5–8]	0.01

**Table 1** Baseline characteristics of patients with mild hypoxemia who survived and patients who died in the hospital (*Continued*)

Characteristics	Survivors, <i>n</i> = 447	Non-survivors, <i>n</i> = 242	<i>P</i> value
FiO <sub>2</sub> , %	40 [39–41]	40 [39–41]	0.83
PaO <sub>2</sub> /FiO <sub>2</sub> , mmHg	272 [22–324]	248 [213–294]	< 0.01
Tidal volume, ml/kg PBW	7.3 [6.3–8.6]	7.3 [6.4–8.5]	0.88
Respiratory rate, per minute	18 [15–22]	19 [15–25]	0.04
PaO <sub>2</sub> , mmHg	107 [90–133]	101 [88–130]	0.09
PaCO <sub>2</sub> , mmHg	41 [37–46]	39 [34–44]	< 0.01
Dead space fraction	0.1 [0–0.2]	0.1 [0–0.2]	0.04
Use of vasopressors	218 (49)	127 (52)	< 0.01

APACHE acute physiology and chronic health evaluation, COPD chronic obstructive pulmonary disease, IQR interquartile range, PBW predicted body weight, PEEP positive end-expiratory pressure

### Secondary outcomes

Overall, all-cause ICU mortality was 25% (169/689) and all-cause 90-day mortality was 42.2% (291/689). The median number of days that patients were free from invasive mechanical ventilatory support and alive at day 28 was 21 [IQR 0–25] days; the median number of days that patients were outside the ICU and alive at day 28 was 22 [IQR 18–25] days. These secondary outcomes were similar in the four classification groups at hypoxemia onset. In line with the change in risk for all-cause in-hospital mortality, reclassification at 24 h resulted in groups with increasing risks for ICU- and 90-day mortality, and decreasing numbers of ventilator-free and ICU-free days and alive at day 28 from groups I to IV (Table 4).

### Discussion

The findings of this post hoc analysis can be summarized as follows: (a) classification of invasively ventilated patients at onset of mild hypoxemia using predefined PaO<sub>2</sub>/FiO<sub>2</sub> and PEEP cutoffs has no predictive value and (b) reclassification 24 h later using the

**Table 2** Main characteristics of patients with hypoxemia classified 24 h after onset of hypoxemia

Characteristics	Group I, <i>n</i> = 296	Group II, <i>n</i> = 96	Group III, <i>n</i> = 177	Group IV, <i>n</i> = 120	<i>P</i> value
APACHE IV score, median [IQR]	76 [59–97]	77 [60–97]	80 [62–98]	85.5 [62–111]	0.06
Age, median [IQR]	62 [49–70]	62 [50–72]	64 [54–72]	62 [53–72]	0.26
Gender, male, <i>n</i> (%)	183 (62)	62 (65)	116 (66)	80 (67)	0.74
<b>Ventilation parameters, median [IQR]</b>					
Maximum airway pressure, cm H <sub>2</sub> O	16 [13–19]	21 [18–24]	16 [13–20]	22 [19–27]	< 0.01
PEEP, cm H <sub>2</sub> O	5 [5–5]	8 [6–8]	5 [5–5]	8 [7–10]	< 0.01
FiO <sub>2</sub> , %	40 [35–41]	40 [40–41]	40 [40–41]	41 [40–50]	< 0.01
PaO <sub>2</sub> /FiO <sub>2</sub> , mmHg	303 [280–353]	294 [267–339]	212 [190–233]	211 [165–226]	< 0.01
Tidal volume, ml/kg PBW	7.3 [6.4–8.5]	7.3 [6.3–8.4]	7.3 [6.4–8.6]	7.3 [6.5–9]	0.87
Respiratory rate, per minute	17 [14–22]	18 [15–21]	19 [15–23]	18 [15–24]	0.15
PaO <sub>2</sub> , mmHg	120 [105–144]	126 [111–155]	90 [78–98]	94 [82–103]	< 0.01
PaCO <sub>2</sub> , mmHg	39 [35–44]	41 [36–45]	42 [37–48]	41 [36–48]	0.01

APACHE acute physiology and chronic health evaluation, IQR interquartile range, PBW predicted body weight, PEEP positive end-expiratory pressure

**Table 3** Intergroup comparisons for hospital mortality at onset of hypoxemia and after 24 h

Hospital mortality	At onset		After 24 h	
	OR (95% CI)	P value	OR (95% CI)	P value
Group I vs. II	0.87 (0.43–1.74)	1.00	1.00 (0.51–1.98)	0.97
Group I vs. III	0.79 (0.46–1.34)	1.00	0.73 (0.43–1.24)	0.37
Group I vs. IV	0.97 (0.53–1.74)	1.00	0.48 (0.26–0.86)	< 0.01
Group II vs. III	0.91 (0.46–1.79)	1.00	0.72 (0.35–1.48)	0.48
Group II vs. IV	1.10 (0.53–2.28)	1.00	0.47 (0.22–1.02)	0.05
Group III vs. IV	1.22 (0.68–2.16)	1.00	0.65 (0.34–1.23)	0.32

OR odds ratio, CI confidence interval

same predefined cutoffs increases the predictive accuracy for clinically important outcomes, and the improvement outcome prediction was found for all five outcomes, i.e., all-cause in-hospital-, ICU-, and 90-day mortality, and the number of ventilator and ICU-free days.

Hypoxemia is a heterogeneous “syndrome” at onset and a second look after 24 h of standard care enables better prognostication. This approach is not new. Indeed, one retrospective analysis of a randomized controlled trial in ARDS patients [15] and one prospective European study in 38 ICUs [16] showed that an improvement in PaO<sub>2</sub>/FiO<sub>2</sub> within 24 h of standard care is a better predictor of survival than PaO<sub>2</sub>/FiO<sub>2</sub> at ARDS onset. Similar findings came from studies in pediatric cohorts [8, 17]. The value of reclassification after 24 h compared to stratification at onset was also illustrated by the simple fact that two-third of patients do no longer fulfil the criteria for moderate or severe ARDS at the moment of reassessment [18], and these patients have much better outcomes [19]. The present findings mirror those from two recent investigations in patients with moderate or severe ARDS [6, 7], even though reason for hypoxemia in the present study was very different from these last two studies.

The results of the present study provide additional insight in the predictive value of easy to capture respiratory data captured after 24 h of standard care in invasively

**Table 4** All-cause in-hospital mortality in groups based on predefined PaO<sub>2</sub>/FiO<sub>2</sub> and PEEP cutoffs at hypoxemia onset and after 24 h

At onset	Group I, n = 216	Group II, n = 92	Group III, n = 223	Group IV, n = 158	P value for trend
Hospital mortality, n (%)	71 (32.9)	33 (35.9)	85 (38.1)	53 (33.5)	0.65
ICU mortality, n (%)	50 (23.1)	25 (27.2)	59 (26.5)	35 (22.2)	0.99
90-day mortality, n (%)	86 (39.8)	36 (39.1)	103 (46.2)	66 (41.8)	0.40
VFD28, days [IQR]	22 [5–25]	22 [0–24]	21 [0–25]	21 [3–25]	0.28 <sup>#</sup>
ICUFD28, days [IQR]	23 [19–25]	22 [18–24]	22 [18–25]	22 [17–24]	0.09 <sup>#</sup>
At 24 h	Group I, n = 296	Group II, n = 96	Group III, n = 177	Group IV, n = 120	P value for trend
Hospital mortality, n (%)	90 (30.4)	29 (30.2)	66 (37.3)	57 (47.5)	< 0.01
ICU mortality, n (%)	54 (18.2)	19 (19.8)	51 (28.8)	45 (37.5)	< 0.01
90-day mortality, n (%)	119 (40.2)	33 (34.4)	75 (42.4)	64 (53.3)	0.03
VFD28, days [IQR]	23 [14–25]	21 [4–24]	22 [0–25]	16 [0–23]	< 0.01 <sup>#</sup>
ICUFD28, days [IQR]	22 [19–25]	21 [15–25]	22 [19–25]	22 [15–25]	0.02 <sup>#</sup>

<sup>#</sup>A P value for linear regression was calculated

ICU intensive care unit, VFD28 ventilator-free days and alive at day 28, ICUFD28 ICU-free days and live at day 28

ventilated ICU patients that is new for patients suffering from hypoxemia not related to ARDS, patients that have not been studied well so far. If reclassification of patients improves outcome prediction, this would be of value for ICU physicians for determining a patients' prognosis and setting therapeutic targets, but also to enrich study population by enrolling more homogeneous groups of patients, i.e., with similar prognosis in clinical research.

One salient finding is that the hospital mortality in our cohort was a staggering 35%, which is markedly similar to patients with mild ARDS in the recent "The large observational study to understand the global impact of severe acute respiratory failure" (LUNG SAFE) [1], and also similar to the 31% mortality in patients that had quickly resolving ARDS in a secondary analysis of the same study [9]. Beforehand, we expected patients without ARDS to have lower mortality rates than those with ARDS. However, it should be stated that the present analysis involved a highly specific group. Indeed, patients who were no longer ventilated after 24 h were not included, effectively excluding patients with an easily reversible cause for hypoxemia who were already extubated after 24 h. These are also the patients that have a better expected outcome. Of note, none of the patients in the present cohort developed ARDS. This is in line with another report on a slightly different subgroup captured in the database of the MARS study and also with a recent randomized clinical trial in patients without ARDS but a low  $\text{PaO}_2/\text{FiO}_2$  [20, 21]. Also, more than 50% of the patients ended up in another group when reclassified at 24 h, except for the patients in group I.

Strengths of the present study include its prospective nature of collection and follow-up of data in a large cohort of critically ill patients. A dedicated team of well-trained researchers scored patients daily. This resulted in detailed documentation and validation of ICU events in clinical practice making sure that periods of hypoxemia were not missed, and patients were adequately scored for having ARDS or not. We included a group with a wide variety for reasons for invasive ventilation, increasing external validity. Finally, follow-up was nearly complete.

This study is limited by some specific issues; one important limitation is that patients who were extubated within 24 h or who died within 24 h are not included in this analysis; however, in these patients, classification for outcome is much less relevant. Second, patients who developed hypoxemia after the first day were not included in this study; hence, our findings do not apply for patients with mild hypoxemia due to, e.g., fluid overload during stay in ICU, weaning or any other event that happens later in the course of the admission. Third, some cases of hypoxemia still could have been missed or even misclassified. For instance, the performance of arterial blood gas analyses was not protocolized on predefined time points, although arterial blood gas analyses were performed often, up to every 4 h. Fourth, notwithstanding the specific selection criteria for inclusion, this cohort includes patients with many different underlying etiologies for the hypoxemia, which makes targeting this group with a specific therapy difficult/unlikely. Fifth, as no reliable information on fluid administration was available, we cannot rule out the potential influence of applied fluid regimens on the current findings. Similarly, we lacked data on the etiology of hypoxemia or reason to intubate, and this is a shortcoming for the interpretation. Seventh, our results might be biased to selection for admission to the two tertiary care hospitals in the Netherlands. Any difference in ICU admission practice between countries or institutions might limit the generalizability of the presented results.

## Conclusion

Compared to classification using predefined cutoffs for PaO<sub>2</sub>/FiO<sub>2</sub> and PEEP at onset of hypoxemia, reclassification after 24 h of standard care using the same cutoffs improves classification for outcome in ICU patients who develop hypoxemia not explained by ARDS.

## Abbreviations

APACHE: Acute physiology and chronic health evaluation; ARDS: Acute respiratory distress syndrome; FiO<sub>2</sub>: Fraction of inspired oxygen; ICU: Intensive care unit; IQR: Interquartile range; MARS: "Molecular Diagnosis and Risk Stratification of Sepsis" study; PaO<sub>2</sub>: Arterial oxygen partial pressure; PaO<sub>2</sub>/FiO<sub>2</sub>: Arterial oxygen partial pressure to fractional inspired oxygen ratio; PEEP: Positive end-expiratory pressure; SD: Standard deviation

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## Authors' contributions

FDS, LDB, and MJS: study design, data collection, data analysis, data interpretation, and writing. LRS, DO, and OLC: data collection, data analysis, data interpretation, and writing. GA and GC: study design, data analysis, data interpretation, and writing. All authors read and approved the final manuscript.

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## Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

Inclusion in the MARS study was with an opt-out consent method approved by the Institutional Review Board of the UMCU with ID no. 10-056C on June 16, 2010. The MARS study was conducted in accordance to the principles of the Declaration of Helsinki.

## Consent for publication

Not applicable

## Competing interests

None

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