Oxygenation derangements after subarachnoid hemorrhage: incidence and impact on the outcome. Data from a large multicenter, retrospective study.

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Research

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Abstract

Background

Hypoxemia and hyperoxemia are frequent after acute subarachnoid hemorrhage (aSAH) and are associated with an increase in morbidity and mortality. Among the pulmonary complications causing oxygen derangements, acute respiratory distress syndrome (ARDS) seems to be crucial, with a reported incidence ranging from 11 to 50%.

Methods

We designed a multicentric, retrospective cohort study in tree intensive care in Europe. We collected data between January 2009 and December 2017. We included adult patients (≥18 years) with a diagnosis of aSAH. Hypoxemia was defined as PaO_2 <60mmHg, mild hyperoxemia as PaO_2>120mmHg, and severe hyperoxemia as PaO_2>200mmHg. The primary aim of this study was to assess the incidence of episodes of hypoxemia, hyperoxemia, and the oxygen variability values (calculated as the daily difference between the highest and the lowest arterial partial pressure of oxygen (PaO_2)) during the first week after the intensive care unit (ICU) admission. Secondary aims included the evaluation of the incidence of ARDS according to the Berlin criteria, and the assessment of the effect of oxygen derangements on patients' outcomes.

Results

855 patients fulfilled the inclusion criteria. 6.4% of the patients presented at least one episode of hypoxemia (PaO_2 <60mmHg), 56.6% of mild hyperoxemia (PaO_2 >120mmHg), and 16.8% of severe hyperoxemia (PaO_2 >200mmHg). The cumulative incidence of ARDS resulted in 2.2% on the first day since ICU admission, 3.2% by three days, and 3.6% by seven days. A lower Glasgow Coma Scale score (GCS) at admission, longer duration of mechanical ventilation, higher PaO_2 variability, hypoxemia, and ARDS occurrence were independently associated with poor outcome.

Conclusions

Hypoxemia and hyperoxemia episodes are frequent in the first 7-days of ICU stay after aSAH, whereas ARDS has a low incidence. The severity of aSAH but also ARDS occurrence, oxygenation parameters, and duration of MV are associated with patients' outcomes

Introduction

Over the last years, attention has risen towards the levels of oxygenation as an essential determinant of secondary brain injury [1–4]. The deleterious consequences of hypoxemia, (the presence of a partial pressure of oxygen (PaO_2) < 60 mmHg) on the patients' outcome, are well known [5]. More recently, research has also focused on the role of hyperoxemia. In fact, PaO_2 levels > 100 mmHg seem to have

deleterious effects on outcome in critically ill patients overall [6, 7] and the threshold changes only slightly in specific subpopulations such as post-cardiac arrest (PaO_2 levels > 120 mmHg) [8, 9] or aneurysmal subarachnoid hemorrhage (aSAH) (PaO_2 > 200 mmHg) patients [10]. Moreover, the concept of PaO_2 variability, defined as the daily difference between the highest and the lowest PaO_2 values, has recently been identified as a potential surrogate marker for relative ischemia-reperfusion injury [11, 12].

Pulmonary complications causing oxygen derangements after aSAH are frequent and associated with an increase in morbidity and mortality [13], with the worst clinical manifestation being acute respiratory distress syndrome (ARDS) [14]. The reported incidence of ARDS in aSAH patients ranges from 11 to 50% [4, 13, 15, 16]. This heterogeneity could be explained by the absence of standardized treatment protocols, by differences in center policies, or by the use of different ARDS definitions. The Berlin Criteria [17], an updated definition for ARDS aimed to simplify the diagnosis and better prognosticate outcome, has never been applied to the aSAH population.

Altogether, the optimal oxygenation strategies (i.e., both oxygen dose administration and PaO_2 target) remain unclear in aSAH patients.

We, therefore, conducted a multicenter, retrospective, international study, including a large cohort of patients with aSAH, to assess the incidence of oxygen derangements during the first week after intensive care unit (ICU) admission.

Methods

Study cohort

This multicenter retrospective study includes patients with aSAH admitted to the Neuro-intensive care unit (NICU) of the "San Gerardo" hospital in Monza, the NICU of the "Medical University Hospital" of Innsbruck and the medical-surgical ICU of the "Erasme Hospital (ULB)" in Bruxelles between January 2009 and December 2017.

Inclusion criteria were:

- age ≥18 years;
- a diagnosis of aSAH confirmed by a Computed Tomography (CT) scan and by an angio-CT or angiography;
- admission to an ICU involved in the study.

Exclusion criteria were:

- age < 18 years;
- non-aneurysmal SAH;
- brain-death.

Aims of the study

The aims of this study were:

- to assess the incidence of episodes of hypoxemia, hyperoxemia, and PaO_2 variability during the first week from ICU admission;
- to assess the incidence of ARDS, according to the Berlin Criteria;
- to evaluate the effect of oxygen derangements on patients' outcomes.

Data collection

Patients' characteristics

We used the electronic data systems of each center to collect data regarding the patients' previous medical history, including age, smoking habits, and pre-injury comorbidities (e.g., hypertension and chronic obstructive pulmonary disease history). We assessed the Glasgow Coma Scale score (GCS) [20] on admission and the World Federation of Neurosurgical Societies grading system for aSAH (WFNS) [21] for each patient according to their medical records. We recorded the modified Fisher score (mFisher) [22], the arteriography or angio-CT findings (such as aneurysm location), the information regarding the aneurysm treatment (if surgical or endovascular procedure), and we noted whether and how the invasive intracranial pressure was monitored (through an external ventricular drain (EVD) or an intraparenchymal catheter). We assessed the neurological outcome through the Glasgow Outcome Score (GOS) [23] and the modified Rankin scale (mRS) [24] at ICU discharge. We defined an unfavorable outcome as a modified Rankin score $\geq$3 or GOS $\leq$3. We also recorded the length of mechanical ventilation in hours and ICU length of stay (LOS) in days.

Ventilation and oxygenation data

For each patient, we collected data regarding oxygenation, ventilator settings (such as tidal volume (TV) and positive end-expiratory pressure (PEEP)), and arterial blood gases analysis (ABG; pH, PaO_2, and partial pressure of carbon dioxide ($PaCO_2$)) at day one, three, and seven from ICU admission. For each variable, we collected the lowest and highest value for each daily time point. At the corresponding time interval, we calculated the lowest values of the ratio of the PaO_2 over the inhaled fraction of oxygen (PaO_2/FiO_2).

Two trained investigators for each center reviewed all chest X-rays independently, checking for the presence of bilateral infiltrates. In case of disagreement, a third investigator was involved in interpreting the radiological findings.

We defined the episodes of hypoxemia as the detection of at least one measurement of PaO_2 <60mmHg on any ABG of each day of observation (one, three, and seven). We analogously defined the hyperoxemia episodes as mild if a PaO_2 >120mmHg and as severe if a PaO_2 >200mmHg was found at least once on

an ABG for each day [25]. We assessed the oxygen variability as the difference between the highest and the lowest PaO_2 values in mmHg during the day.

To evaluate the ARDS incidence in our cohort, we applied the Berlin definition of ARDS [6] that includes:

- onset within one week of a known clinical insult (aSAH);
- the presence of bilateral chest opacities on X-Ray, not entirely explained by effusion, atelectasis, or cardiac failure. Every case was reviewed, in light of results from echocardiography, electrocardiography or both, to rule out the presence of cardiac failure based on cardiac findings;
- the presence of a PaO_2/FiO_2 ratio <300 and
- a PEEP level > 5 cmH_2

When we reached a diagnosis of ARDS, we also assessed whether the same episode lasted for multiple days during the first week of ICU admission, thus avoiding the risk of a repeated diagnosis.

Statistical analysis

We described quantitative variables as the median and interquartile range (IQR), and categorical variables as number and percentage. We used the Fisher's exact test for categorical variables and Wilcoxon tests for continuous variables to compare the characteristics of patients with or without ARDS at ICU admission.

The association between the admission characteristics and the primary outcome, dichotomized as favorable (GOS 4-5, mRS 0-2) or unfavorable (GOS 1-3, mRS 3-5), was first analyzed using Fisher's exact test for categorical values and Wilcoxon test for continuous variables. We then conducted a multivariable logistic regression to adjust on predefined variables according to our hypothesis and previously published models. We included the following factors in the multivariate logistic regression: age, GCS at admission, WFNS score, mFisher scale, ARDS occurrence, mild hyperoxemia episodes, hypoxemia episodes, high PaO_2 variability, and duration of mechanical ventilation. Aspiration pneumonia, the presence of pathological secretions at admission, PEEP values at admission, chest X-ray results, and the administration of neuromuscular blocking. The WFNS score includes the GCS and hence was discarded from the multivariate analysis. We compared the c index of models with and without PaO_2 variability to evaluate its additive value in outcome prediction. Results are presented as Odds ratios with 95% confidence interval.

All tests were two-sided at a 0.05 significance level; we performed the statistical analysis using R, software version 3.5.2 [26].

Results

To the best of our knowledge, this is the most extensive multicenter study describing oxygen derangements after aSAH. For the first time, we assessed the role of both hypoxemia and hyperoxemia in

aSAH patients, including the concept of oxygen variability that could account for unfavorable outcome. Moreover, this is the first study evaluating the occurrence of ARDS using the Berlin definition in this population. The large size of our cohort and the inclusion of three different centers make this study well representative for the evaluation of the incidence and effects on patients' outcomes of respiratory derangements after aSAH.

According to our results:

- episodes of oxygenation derangements, i.e., hyperoxemia and hypoxemia, are frequent in aSAH patients, whereas
- the incidence of ARDS after aSAH reaches only 3.6% within the first week of ICU admission.
- the duration of mechanical ventilation, neurological status at admission (GCS), and PaO_2 variability are all independent factors for unfavorable outcome. We also confirmed that hypoxemia and ARDS are associated with unfavorable outcome after aSAH.

The main goal of mechanical ventilation in aSAH patients is to provide adequate oxygenation and to prevent the risk of hypoxemia, which is a well-known cause of secondary brain injury [30]. The recommended target of oxygenation as per PaO_2 values in brain-injured patients with healthy lungs is > 75 mmHg, whereas in those suffering from ARDS, lower PaO_2 targets (55-80 mmHg) are suggested [19]. Also, oxygenation derangements are frequent, with an incidence ranging from 43% to 92% in aSAH patients [27].

Supplemental oxygen is a fundamental part of the acute management of these patients; however, aggressive treatment of hypoxemia might lead to the patients’ exposure to unnecessarily high levels of FiO_2, even higher than the values strictly necessary to maintain physiologic values of PaO_2, sometimes for a prolonged amount of time.

Although moderate hyperoxemia can increase cerebral oxygenation as measured by near-infrared spectrometry (NIRS), its clinical implications remain unclear [28, 29]. Indeed, hyperoxemia can have detrimental effects on the patients' outcome by several pathophysiological mechanisms, including oxidative damage and an increase in reactive oxygen species production, deriving from high tissue oxygen tension with consequent mitochondrial damage and lipid peroxidation, leading to neuronal cells apoptosis. Several cohort studies support the hypothesis that hyperoxemia could be detrimental in the emergency room [30] and after cardiac arrest [9]. Although the effects are particularly pronounced following long-term exposition to high PaO_2 levels, several studies suggest that even short term hyperoxemia can lead to increased mortality and morbidity, especially in brain-injured patients [31, 32].

A randomized trial [18] which compared two targets of PaO_2 (70 vs. 100 mm Hg or arterial oxygen saturation (SaO_2) between 94% and 98% vs. SaO_2 values between 97% and 100%) found that a conservative target for oxygen therapy is associated with reduced ICU mortality (absolute risk reduction

of 0.086 [95% CI, 0.017-0.150]). More recently, a retrospective analysis of an extensive database confirmed these results for severe but not for mild hyperoxemia after cardiac arrest [28].

We also found that PaO_2 variability was independently associated with poor outcome. PaO_2 variability could cause the so-called “reperfusion injury,” defined as the tissue damage resulting from the restoring of appropriate oxygen and blood supply after a period of hypoxemia [39]. Low oxygen arterial pressure is responsible for tissue hypoxemia or ischemia, which can be followed by reperfusion upon PaO_2 increase. Such a reperfusion mechanism could increase neuro-inflammation and brain damage [33]. Thus, PaO_2 variability could be a surrogate marker for relative ischemia-reperfusion injury in the brain, which could cause secondary brain injury. Indeed, in pediatric intensive care, oxygen variability measured on the plethysmography has recently been shown to predict chronic lung disease [11, 12] or the need for hospitalization [12].

ARDS after aSAH can be consequent to several factors, including neurogenic pulmonary edema (NPE), aspiration pneumonia, or ventilator-associated pneumonia. In our study, we did not investigate the etiology of ARDS, but the incidence of aspiration pneumonia and the presence of pathological pulmonary secretions was similar in patients with and without ARDS. The peak of incidence of ARDS was in the first 24 hours, corresponding to that of NPE, thus suggesting that probably NPE was the leading cause of ARDS in our cohort.

A retrospective study reported an incidence of PaO_2/FiO_2 ratio <300 in nearly one-third of patients with aSAH (27%) [13]. However, other authors suggested that the prevalence of ARDS is much lower, ranging from 4 to 18% [34, 35]. The results of our study suggest that the incidence of ARDS is even lower when compared to previous literature [1,3-5]. The reason could be related to the increasing application of protective ventilation strategies [20] in our institutions over the last years. The beneficial effect of protective lung ventilation and respiratory strategies are well established in the general ICU population and the operating room [36, 37]. However, the application of these techniques in neuro-critical care patients is contrasting because of this group’s specific therapeutic needs and ventilator targets, and for the potential risks of lung-protective ventilation strategies on intracranial pressure and cerebral perfusion pressure. However, recent studies support the use of protective strategies and, in particular, of low driving pressure and low tidal volumes even in brain-injured patients[38].

Of note, we chose to evaluate the ARDS incidence according to the daily worst PaO_2/FiO_2 value. Thus, we might have overestimated the incidence of ARDS, as daily lowest $PaO_2/FiO2$ could be the result of temporary episodes of hypoxemia such as those occurring during an atelectasis episode, during the transports to the radiologic suite, or during an angiographic procedure.

We also showed that patients with ARDS have more frequent episodes of hyperoxemia, a trend towards more frequent episodes of hypoxemia, and a subsequent increased PaO_2 variability. Several causes could explain the high PaO_2 variability found in ARDS patients. Aggressive treatment of hypoxemia might have led to higher levels of FiO_2 and, therefore, high levels of PaO_2. Also, patients with ARDS are more

susceptible to episodes of derecruitment, atelectasis, and desaturation, promptly treated with high FiO_2 and recruitment maneuvers by the attending physician, causing rapid changes in oxygenation values.

One of the limits of this hypothesis is that the PaO_2 variability might represent the combined predictive value of both hypoxemia and hyperoxemia and therefore present a better predictive value than each variable alone. Nevertheless, in the multivariate model, hypoxemia had a modest predictive value, and PaO_2 variability presented a predictive value independent from hypo- and hyperoxemia, supporting its independent impact on the outcome.

Limitations

Several limitations to this study need to be mentioned. First, we evaluated ARDS secondary to subarachnoid hemorrhage within the first seven days after the ICU admission, evaluating its occurrence on days one, three, and seven. The median ventilation time in our cohort was 2.00 [0.00, 11.00] days; therefore, patients could have developed ARDS afterward, which could result in an underestimation of the real incidence of ARDS in this group of patients.

Second, we focused on the early outcome after aSAH, at ICU discharge. However, the evaluation of long-term neurological outcome in aSAH would have provided a much stronger message to our study. Third, we have reported associations but not causality, due to the retrospective observational design of this study; moreover, a retrospective data collection resulted in the lack of precise and complete data regarding ventilation and other confounders that might have influenced the patients' outcome. Finally, we evaluated the daily PaO_2 through discontinuous arterial blood gases analysis that might represent less accurately the PaO_2 variability when compared to continuous measures.

Discussion

To the best of our knowledge, this is the most extensive multicenter study describing oxygen derangements after aSAH. For the first time, we assessed the role of both hypoxemia and hyperoxemia in aSAH patients, including the concept of oxygen variability that could account for unfavorable outcome. Moreover, this is the first study evaluating the occurrence of ARDS using the Berlin definition in this population. The large size of our cohort and the inclusion of three different centers make this study well representative for the evaluation of the incidence and effects on patients' outcomes of respiratory derangements after aSAH.

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Conclusion

Our results show that episodes of hypo- and hyperoxemia are frequent in aSAH patients. Also, ARDS has a low incidence in the first seven-day period of ICU admission after aSAH, and this could be due to the systematic use of protective ventilation strategies in our institutions. The most important predictors of outcome at ICU discharge are the severity of aSAH, the duration of mechanical ventilation, the ARDS occurrence, and the oxygenation parameters. The precise impact of hypoxemia, hyperoxemia, and oxygen variability needs to be further evaluated in interventional trials.

Declarations

Ethics approval and consent to participate

The local ethics committee of each center approved the conduct of the study and waived the need for informed consent due to the retrospective nature of the study. In Monza: Comitato Etico Brianza, protocol number 3115; in Innsbruck: The Medical University of Innsbruck, protocol number AM4091-292/4.6; in Bruxelles: Erasme Hospital, protocol number P2018/128.

Consent for publication

Not applicable.

Availability of data and materials

The anonymized datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no conflict of interest for this manuscript.

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No external funding has been obtained for this research.

Authors' contributions

G.C., A.M., C.R. contributed to the conception and design of the study. A.M, A.V, C.I., V.R., F.T., R.H., E.G.B. contributed to the acquisition of data for the work. A.M. and P.R. performed the statistical analysis with the collaboration of G.C. and C.R.; A.M., C.R., C.I, and G.C. wrote the first draft of the manuscript. All the authors revised and approved the final version of the manuscript.

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None

Abbreviations

- ABG: arterial blood gas analysis;
- ARDS: acute respiratory distress syndrome;
- aSAH: aneurismal subarachnoid hemorrhage;
- cmH_2O: centimeters of water;
- EVD: external ventricular drain;
- FiO_2: inhaled oxygen fraction;
- GCS: Glasgow coma score;
- GOS: Glasgow outcome score;
- ICU: intensive care unit;
- IQR: interquartile range;
- LOS: length of stay;
- mFisher: modified Fisher score;
- mmHg: millimeters of mercury;
- mRS: modified Rankin scale;
- NICU: neurointensive care unit;
- NIRS: near-infrared spectrometry;
- NPE: neurogenic pulmonary edema;
- $PaCO_2$: arterial partial pressure of carbon dioxide;
- PaO_2: arterial partial pressure of oxygen;
- PaO_2 variability: daily oxygen variability;
- PaO_2/FiO_2: the ratio of the arterial partial pressure of oxygen over the inhaled fraction of oxygen;

- PEEP: positive end-expiratory pressure;
- SaO_2: arterial oxygen saturation;
- TV: tidal volume;
- VAP: ventilator-associated pneumonia;
- WFNS: World Federation of Neurosurgical Societies grading system for aSAH.

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Tables

Table 1

General characteristics of patients with a diagnosis of subarachnoid hemorrhage, at admittance to the neurointensive care unit. ARDS: Acute Respiratory Distress Syndrome; COPD: chronic obstructive pulmonary lung disease; EVD: external ventricular drain; ICP: intracranial pressure; mFisher: modified Fisher score; WFNS: World Federation of Neurosurgical Societies grading system for aSAH.

	Overall	Patients without ARDS	Patients with ARDS	p	Missing
n	855	824 (96.4%)	31 (3.6%)		
Age years (median [IQR])	56 [47, 67]	56 [47, 67]	59 [49, 67]	0.408	1.0
Sex n (%)	347 (40.7)	331 (40.3)	16 (53.3)	0.214	0.9
Smoking History n (%)	214 (25.3)	210 (25.8)	4 (13.3)	0.185	1.7
COPD n (%)	44 (5.2)	41 (5.0)	3 (10.0)	0.431	1.6
High Blood Pressure n (%)	378 (44.6)	362 (44.3)	16 (53.3)	0.426	1.4
Chronic Kidney Failure n (%)	31 (3.7)	29 (3.6)	2 (6.7)	0.692	1.6
Re-bleeding n (%)	84 (9.9)	82 (10.0)	2 (6.7)	0.774	1.0
Glasgow motor score at admission (median [IQR])	6 [2, 6]	6 [2, 6]	5 [2, 6]	0.051	1.3
Glasgow coma scale at admission (median [IQR])	14 [5, 15]	14 [5, 15]	7 [4, 14]	0.092	1.0
WFNS score (median [IQR])	2 [1, 5]	2 [1, 5]	4 [2, 5]	0.045	0.9
mFisher (median [IQR])	4 [3, 4]	4 [3, 4]	4 [4, 4]	0.004	0.9
Posterior circulation n (%)	151 (17.7)	148 (18.0)	3 (10.0)	0.376	0.9
Endovascular treatment n (%)	408 (47.9)	394 (48.0)	14 (46.7)	1.000	1.0
Surgery n (%)	275 (32.3)	258 (31.4)	17 (56.7)	0.007	1.0
ICP catheter insertion n (%)	272 (31.9)	250 (30.4)	22 (73.3)	<0.001	0.8
EVD insertion n (%)	373 (43.7)	350 (42.5)	23 (76.7)	<0.001	0.8

Table 2

Characteristics of patients with a diagnosis of subarachnoid hemorrhage according to the presence or absence of a concomitant acute respiratory distress syndrome. An adverse outcome is defined as the presence of a modified Rankin score > 2 or of a Glasgow outcome score <4. ICU: Intensive Care Unit; IQR: interquartile range; SD: standard deviation; PaO_2/FiO_2: the ratio between the arterial partial pressure in oxygen (PaO_2) in mmHg and the inhaled fraction of oxygen (FiO_2).

	Overall	No ARDS	ARDS	p	Missing
n	855	824	31		
Bilateral chest infiltrates	42 (4.9)	11 (1.3)	31 (100.0)	<0.001	0.0
Highest temperature ˚C (mean (SD))	37.68 (0.90)	37.70 (0.87)	37.29 (1.44)	0.014	1.3
Pathologic secretions n (%)	281 (32.9)	267 (32.2)	14 (45.2)	0.189	0.0
White blood count day 0, as G/L (median [IQR])	11.6 [9.2, 14.4]	11.6 [9.1, 14.2]	12.6 [10.0, 17.6]	0.173	15.9
Highest PaO_2/FiO_2 ratio (median [IQR])	411 [346, 474]	413 [350, 475]	371 [254, 444]	0.021	14.2
Lowest PaO_2/FiO_2 ratio (median [IQR])	230 [168, 305]	234 [173, 311]	150 [118, 179]	<0.001	14.2
Neuromuscular blockage (%)	129 (15.6)	121 (15.2)	8 (26.7)	0.150	4.1
Highest PEEP cm H_2O (median [IQR])	8 [5, 9]	8 [5, 9]	10 [7, 10]	0.010	32.4
Highest tidal volume mL (median [IQR])	520 [482, 598]	524 [487, 600]	487 [420, 510]	<0.001	37.7
Lowest tidal volume mL (median [IQR])	460 [410, 500]	460 [410, 500]	420 [400, 460]	0.099	41.5
Highest PaO_2 mmHg (median [IQR])	127 [103, 181]	127 [102, 178]	168 [125, 209]	0.019	0.0
Lowest PaO_2 mmHg (median [IQR])	80 [70, 99]	80 [70, 99]	74 [63, 80]	0.001	0.0
Hypoxemia <60 mmHg n (%)	61 (7.1)	56 (6.8)	5 (16.1)	0.104	0.0
Hyperoxemia >120 mmHg n (%)	484 (56.6)	460 (55.8)	24 (77.4)	0.026	0.0
Hyperoxemia >200 mmHg n (%)	144 (16.8)	135 (16.4)	9 (29.0)	0.105	0.0
PaO_2 variability mmHg (median [IQR])	33 [19, 53]	33 [18, 52]	51 [28, 75]	0.002	16.4
Prolonged ventilation (7days) n (%)	301 (35.2)	286 (34.7)	15 (48.4)	0.169	0.6
Ventilation Time (median [IQR])	2 [0, 11]	2 [0, 11]	6 [2, 15]	0.002	0.6
ICU length of stay days (median [IQR])	11 [4, 21]	11 [4, 21]	9 [2, 17]	0.198	0.6
Adverse outcome n (%)	407 (47.6)	384 (46.4)	23 (74.2)	0.005	0.0

Table 3

Outcomes of patients with a diagnosis of subarachnoid hemorrhage admitted to the intensive care unit. COPD: chronic obstructive pulmonary lung disease; EVD: external ventricular drain; ICP: intracranial pressure; mFisher: modified Fisher score; PaO_2/FiO_2: the ratio between the arterial partial pressure in oxygen (PaO_2) in mmHg and the inhaled fraction of oxygen (FiO_2); WFNS: World Federation of Neurosurgical Societies grading system for aSAH.

	Overall	Good Outcome	Bad Outcome	p	Missing
n (%)	855	448 (52.3)	407 (47.7)		(%)
Age years (median [IQR])	56 [47, 67]	54 [46, 66]	58 [49, 68]	<0.001	1.0
Sex n (%)	347 (40.7)	188 (42.2)	159 (39.2)	0.414	0.9
Smoking History n (%)	214 (25.3)	101 (22.7)	113 (28.2)	0.083	1.7
BPCO n (%)	44 (5.2)	17 (3.8)	27 (6.7)	0.080	1.6
High Blood Pressure n (%)	378 (44.6)	186 (41.8)	192 (47.6)	0.101	1.4
Chronic Kidney Failure n (%)	31 (3.7)	13 (2.9)	18 (4.5)	0.304	1.6
Rebleeding n (%)	84 (9.9)	41 (9.2)	43 (10.6)	0.577	1.0
Glasgow motor score at admission (median [IQR])	6 [2, 6]	6 [5, 6]	5 [1, 6]	<0.001	1.3
Glasgow coma scale at admission (median [IQR])	14 [5, 15]	14 [9, 15]	9 [3, 15]	<0.001	1.0
WFNS (median [IQR])	2 [1, 5]	2 [1, 4]	4 [1, 5]	<0.001	0.9
mFISHER (median [IQR])	4 [3, 4]	4 [3, 4]	4 [3, 4]	<0.001	0.9
Posterior circulation n (%)	151 (17.7)	77 (17.3)	74 (18.2)	0.781	0.9
Coiling n (%)	408 (47.9)	222 (49.8)	186 (45.9)	0.292	1.0
Surgery n (%)	275 (32.3)	119 (26.7)	156 (38.5)	<0.001	1.0
ICP catheter n (%)	272 (31.9)	103 (23.0)	169 (41.6)	<0.001	0.8
EVD insertion n (%)	373 (43.7)	166 (37.1)	207 (51.0)	<0.001	0.8
Aspiration Pneumonia n (%)	57 (6.7)	18 (4.0)	39 (9.6)	0.002	0.9
ARDS diagnosis n (%)	31 (3.6)	8 (1.8)	23 (5.6)	0.005	0.0
Bilateral chest infiltrates	42 (4.9)	12 (2.7)	30 (7.3)	0.003	0.0
Highest temperature °C (mean (SD))	37.7 (0.90)	37.6 (0.80)	37.8 (0.99)	<0.001	1.3
Pathologic secretions n (%)	281 (32.7)	89 (19.8)	192 (46.8)	<0.001	0.0
White blood cell count day 1 (median [IQR])	11.6 [9.2, 14.4]	11.2 [9.0, 13.5]	12.5 [9.4, 15.5]	0.004	15.9
Highest PaO_2/FiO_2 ratio (median [IQR])	411 [346, 474]	414 [356, 476]	408 [340, 468]	0.209	14.2
Lowest PaO_2/FiO_2 ratio (median [IQR])	230 [168, 305]	261 [189, 336]	209 [153, 260]	<0.001	14.2
Neuromuscular blockage (%)	129 (15.6)	45 (10.7)	84 (20.8)	<0.001	4.1
Highest PEEP cm H_2O (median [IQR])	8 [5, 10]	5 [5, 8]	8 [5, 10]	<0.001	32.4
Highest tidal volume mL (median [IQR])	520 [482, 598]	518 [480, 573]	530 [487, 612]	0.022	37.7
Lowest tidal volume mL (median [IQR])	460 [410, 500]	480 [435, 512]	450 [400, 492]	<0.001	41.5
Highest PaO_2 mmHg (median [IQR])	127 [103, 181]	125 [100, 172]	131 [105, 189]	0.033	0.0
Lowest PaO_2 mmHg (median [IQR])	80 [70, 99]	80 [71, 102]	80 [69, 95]	0.072	0.0
Hypoxemia <60 mmHg n (%)	61 (7.1)	23 (5.1)	38 (9.3)	0.024	0.0
Hyperoxemia >120 mmHg n (%)	484 (56.3)	239 (53.1)	245 (59.8)	0.058	0.0
Hyperoxemia >200 mmHg n (%)	144 (16.7)	62 (13.8)	82 (20.0)	0.019	0.0
PaO_2 variability mmHg (median [IQR])	33.2 [18.7, 53.4]	31.6 [16.9, 49.9]	36.0 [21.1, 55.7]	0.005	16.4
Prolonged ventilation (7 days) n (%)	11 [4, 21]	7 [3, 15]	16 [7, 27]	<0.001	0.6
Ventilation time in hours (median [IQR])	301 (35.2)	88 (19.6)	213 (52.3)	<0.001	0.6
ICU length of stay in days (median [IQR])	2 [0, 11]	1 [0, 3.25]	7 [1, 17]	<0.001	0.6

Table 4

Multivariate model evaluating the risk of an adverse outcome, defined as a modified Rankin score > 2 or as a Glasgow outcome score <4. ARDS: Acute Respiratory Distress Syndrome; mFisher: modified Fisher score; OR: Odds Ratio.

	OR	2.5%	97.5%	p
Ventilation time (per day)	1,07	1,05	1,09	<0,0001
Admission Glasgow Coma Scale (per point)	0,95	0,92	0,98	0,003
PaO_2 variability (per mmHg)	1,01	1,00	1,01	0,022
Hypoxemia occurrence	1,92	1.07	3,50	0,030
ARDS occurrence	2,38	1,03	6,00	0,050
Age (per year)	1,01	1,00	1,02	0,136
Mild hyperoxemia > 120 mmHg	0,80	0,54	1,17	0,254
mFisher	1,01	0,84	1,22	0,915

Figures

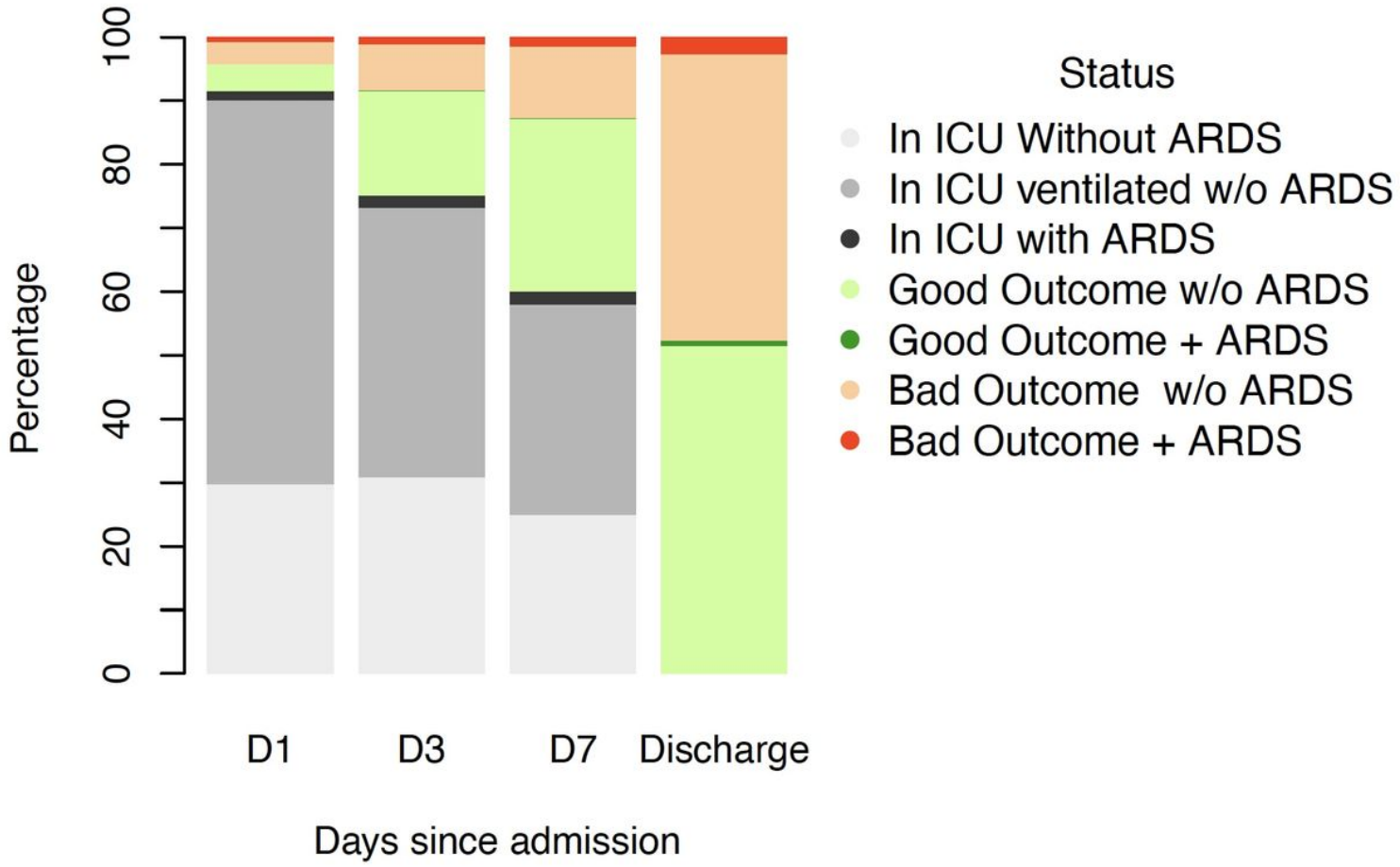

Figure 1

The course of patients admitted to the intensive care unit on days 1, 3, 7, and at discharge. The outcome was evaluated at discharge from the intensive care unit; an adverse outcome was defined as a modified

Rankin score >2 or a Glasgow outcome score <4. Data are presented as percentages of the whole population (n=855). ARDS: acute respiratory distress syndrome; w/o: without.

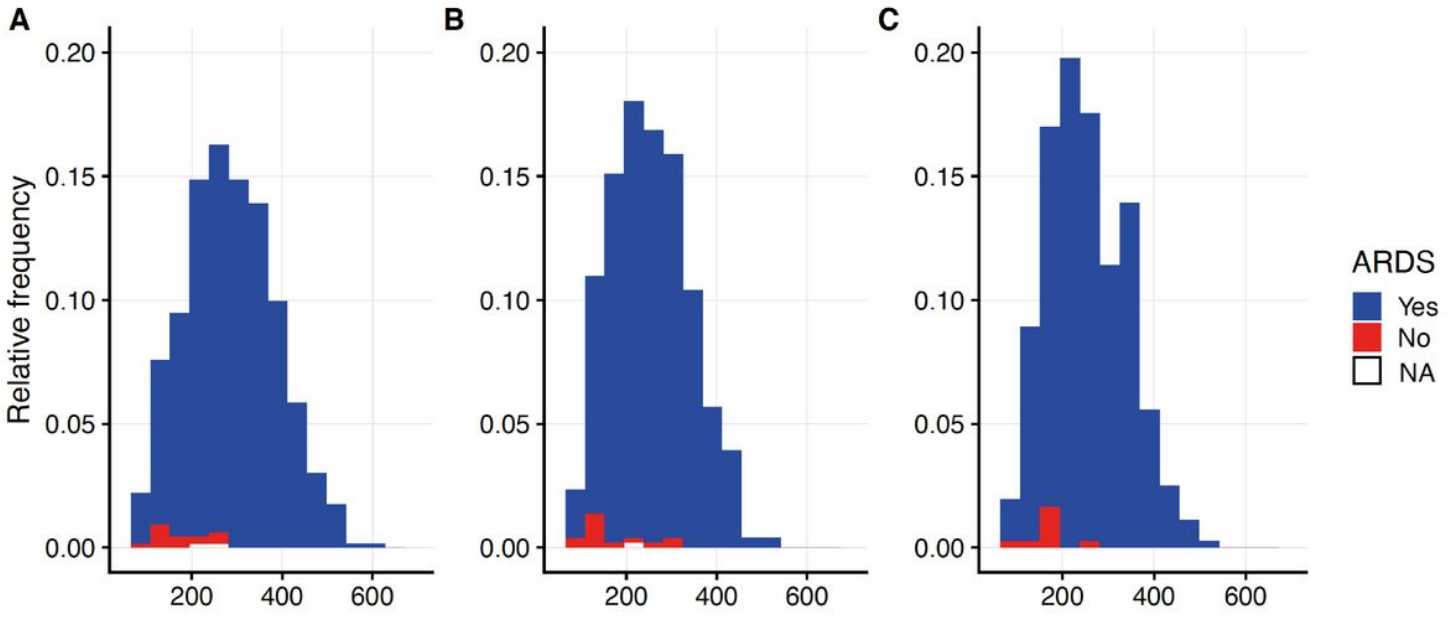

Figure 2

The ratio of arterial partial pressure in oxygen in mmHg and inhaled fraction of oxygen values at days 1, 3, and 7 in patients with and without acute respiratory distress syndrome. X-axis: the ratio between arterial partial pressure in oxygen in mmHg and the inhaled fraction of oxygen. The blue bar represents the patients without acute respiratory distress syndrome and the red bar the patients with a diagnosis of acute respiratory distress syndrome; the white bar represents missing values. Data are presented as relative frequency among the whole population. NA: not available.

Supplementary Files

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