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Hyperoxemia in invasively ventilated COVID—19 patients—Insights from the PRoVENT—COVID study

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KEYWORDS
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Abstract
Objective: We determined the prevalences of hyperoxemia and excessive oxygen use, and the epidemiology, ventilation characteristics and outcomes associated with hyperoxemia in invasively ventilated patients with coronavirus disease 2019 (COVID—19).
Methods: Post hoc analysis of a national, multicentre, observational study in 22 ICUs. Patients were classified in the first two days of invasive ventilation as 'hyperoxemic' or 'normoxemic'. The co—primary endpoints were prevalence of hyperoxemia (PaO_2 > 90 mmHg) and prevalence

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Hyperoxemia;
Normoxemia;
Oxygen management;
Mortality

of excessive oxygen use ($FiO_2 \geq 60\%$ while $PaO_2 > 90$ mmHg or $SpO_2 > 92\%$). Secondary endpoints included ventilator settings and ventilation parameters, duration of ventilation, length of stay (LOS) in ICU and hospital, and mortality in ICU, hospital, and at day 28 and 90. We used propensity matching to control for observed confounding factors that may influence endpoints.

Results: Of 851 COVID−19 patients, 225 (26.4%) were classified as hyperoxemic. Excessive oxygen use occurred in 385 (45.2%) patients. Acute respiratory distress syndrome (ARDS) severity was lowest in hyperoxemic patients. Hyperoxemic patients were ventilated with higher positive end−expiratory pressure (PEEP), while rescue therapies for hypoxemia were applied more often in normoxemic patients. Neither in the unmatched nor in the matched analysis were there differences between hyperoxemic and normoxemic patients with regard to any of the clinical outcomes.

Conclusion: In this cohort of invasively ventilated COVID−19 patients, hyperoxemia occurred often and so did excessive oxygen use. The main differences between hyperoxemic and normoxemic patients were ARDS severity and use of PEEP. Clinical outcomes were not different between hyperoxemic and normoxemic patients.

Introduction

Both severe and moderate hyperoxemia have been reported to be associated with worse outcomes in critically ill patients,[1,2] and high levels of fraction of inspired oxygen (FiO_2) have detrimental effects on lung tissue, causing damage comparable to that seen in acute respiratory distress syndrome (ARDS).[3,4] However, the exact targets of arterial oxygen tension (PaO_2) and FiO_2 remain debated, especially in ARDS patients where the relationship between oxygenation and outcome is complex. One seminal study, named 'OXYGEN−ICU', showed a conservative oxygen strategy targeting PaO_2 of 70−100 mmHg compared with a liberal oxygenation therapy targeting $PaO_2 > 150$ mmHg to improve survival.[5] More recent studies comparing a conservative oxygen strategy with less liberal oxygen strategies, however, failed to show benefit.[6-11]

Coronavirus disease 2019 (COVID−19) is currently the most common form of ARDS, and patients with COVID−19 ARDS almost always experience profound impairments in gas exchange.[12-14] To determine the exact prevalence of hyperoxemia and of excessive oxygen use in invasively ventilated COVID−19 patients, we performed a secondary analysis of a conveniently−sized multicentre observational study, named the 'PRactice of VENTilation in COVID−19' (PRoVENT−COVID).[15] We compared the epidemiology, ventilation characteristics and outcomes in hyperoxemic versus normoxemic patients. We used propensity matching to control for observed confounding factors. The hypothesis was that hyperoxemia and excessive oxygen use occur often in COVID−19 patients under invasive ventilation.

Methods

Study design

Secondary analysis of PRoVENT−COVID, an investigator−initiated, national, multicentre, observational cohort study undertaken at 22 ICUs in the Netherlands. The study protocol of PRoVENT−COVID and the analysis plan for the current analysis have been prepublished[16,17] and the study is registered at clinicaltrials.gov (NCT04346342). Other post−hoc evaluations of PRoVENT−COVID regarding ventilation characteristics and strategies,[15,18,19] and gas exchange,[20,21] were reported earlier.

Patients

Consecutive patients were eligible for participation if they were > 18 years of age, admitted to one of the participating ICUs, and had received invasive ventilation for acute hypoxemic respiratory failure related to COVID−19. COVID−19 was to be confirmed by RT−PCR. For the current analysis, we excluded patients that were transferred from or to a non−participating hospital in the first two days of invasive ventilation, as we could not collect data on gas exchange during these days in those patients, and patients without PaO_2 data on the first two days of invasive ventilation.

Collected data

Patient demographics, medical history, presence and severity of ARDS, and extent of infiltrates on the chest radiography or computed tomography scan was collected at baseline.

Since the first day of ventilation had a flexible length and could range from one minute to 24 hours duration depending on the timing of start of invasive ventilation in the ICU, we merged this day with the second day and named it 'day 1'. The following calendar day was named 'day 2'.

We collected detailed ventilation data at one hour after start of invasive ventilation in the ICU, which could be at arrival if the patients started with invasive ventilation in the normal ward or in the emergency room, or after intubation in the ICU after ICU admission. Thereafter, we collected ventilation data at 08:00, 16:00 and 24:00 hours over the first four days of ventilation. Ventilation data included ventilator settings and ventilation parameters, arterial blood gas analyses results and use of adjunctive therapies for refractory hypoxemia.

We also collected typical aspects of ICU monitoring and care, and common ICU complications. Patients were followed until day 90 for intubation status, ICU− and hospital−discharge, and death.

Exposures

The primary exposure of interest was hyperoxemia on day 1 or day 2 of invasive ventilation, defined as $PaO_2 > 90$ mmHg. Patients were categorized as 'hyperoxemic' if the daily mean PaO_2 was > 90 mmHg, or 'hypoxemic' if the daily mean PaO_2 was ≤ 55 mmHg, on either day 1 or day 2; all other patients were classified as 'normoxemic'. The first PaO_2 value was ignored, because it is plausible that this value could not be affected by FiO_2 titrations by ICU team members.

The secondary exposure of interest was excessive use of oxygen. At each time−point on day 1 and day 2, oxygen use was classified as 'excessive' if FiO_2 was $\geq 60\%$ following a previous blood gas analysis showing $PaO_2 > 90$ mmHg or recorded $SpO_2 > 92\%$.

Outcomes

The co−primary outcomes were the prevalence of hyperoxemia and the prevalence of excessive oxygen use. Secondary outcomes included key ventilator settings and parameters, including tidal volume (V_T), positive end−expiratory pressure (PEEP), driving pressure (ΔP) and respiratory system compliance (Crs), and typical clinical outcomes, including duration of ventilation, length of stay (LOS) in hospital and ICU, and mortality in ICU, hospital, and at day 28 and day 90.

Statistical analysis

Due to the very small number of hypoxemic patients, i.e., 8 out of 851 patients, hypoxemic patients were added to the cohort of normoxemic patients in all analyses.

To assess differences between hyperoxemic and normoxemic patients, Wilcoxon−Mann−Whitney test for continuous data and Fisher exact test for categorical data were used. Ventilation data was reported at three specific moments: 1) at start of ventilation, 2) on day 1, and 3) on day 2. Start of ventilation was based on the measurements collected within the first hour after start of ventilation. As previously mentioned, the measurements of the first flexible calendar day and first full calendar day were merged, and day 1 was based on the means of these measurements. Day 2 was based on the means of the measurements of the following calendar day. Cumulative frequency distributions of V_T, PEEP, ΔP, and Crs are shown for patients categorized as hyperoxemic versus patients that are categorized as normoxemic, at day 1 and at day 2. Locally estimated scatterplot smoothing (LOESS) method was used to inspect the relationship between 28−day mortality and PaO_2 and FiO_2 at day 1 and at day 2.

To further evaluate the associations of outcome with occurrence of hyperoxemia, a propensity matched analysis was performed. For each patient, a propensity score was estimated with logistic regression and used to match hyperoxemic patients to normoxemic patients (1:1) using a caliper of 0.05 standard deviation of the logit of the propensity score and applying nearest matching without replacement. Based on clinical relevance and one previous analysis,[22] the following variables were selected a priori: age, sex, BMI, chronic diseases including heart failure, diabetes mellitus, chronic renal failure, chronic liver failure, chronic pulmonary obstructive disease, active or hematologic neoplasm and immunosuppression, and PaO_2/FiO_2, Crs, total respiratory rate (RR) and bicarbonate at baseline.

Time until extubation is shown in a cumulative distribution plot with death as a competing risk and compared with a Fine−Gray competing risk model. Probability of survival at day 28 and 90 was estimated using Kaplan−Meier curves and compared with a log−rank test.

In a sensitivity analysis, we excluded the hypoxemic patients to check whether there were differences in clinical outcomes.

All analyses were conducted in R v.3.6.1 (R Foundation, Vienna, Austria) and significance level was set at 0.05.

Results

Patients

1122 patients were included in PRoVENT−COVID (Fig. 1). We excluded 271 patients, mainly because of early transfer from or to a non−participating ICU. The remaining 851 patients most often were male (73%) with a median age of 66 [58−72] years, and the majority of patients had moderate to severe ARDS (Table 1).

Prevalence of hyperoxemia and excessive oxygen use

Of 851 patients, 182 (21.4%) patients were hyperoxemic on day 1 and 77 (9.0%) patients were hyperoxemic on day 2. Only 34 (4%) patients were hyperoxemic on both days, but 225 (26.4%) patients were hyperoxemic on either day 1 or day 2 (Fig. 1). eTable 1, eFigure 1 and eResults show group assignments, and daily mean PaO_2 and SpO_2.

Excessive oxygen use occurred at least once in 385 (45.2%) patients. The prevalence was not different between hyperoxemic and normoxemic patients on day 1 but occurred more often in normoxemic patients on day 2 (eTable 2). eTable 1, eFigure 1 and 2, and eResults show group assignments, and daily mean FiO_2. Median daily FiO_2 was slightly lower in hyperoxemic patients on both days.

Patient demographics and ventilation parameters

Moderate to severe ARDS was less often seen in hyperoxemic patients than in normoxemic patients, and hyperoxemic patients had a lower urinary output and a slightly higher plasma lactate at baseline (Table 1).

At start of ventilation, hyperoxemic patients received a similar V_T at a comparable ΔP, and consequently had comparable Crs to normoxemic patients (eTable 1). At start of ventilation, hyperoxemic patients received ventilation with higher PEEP than normoxemic patients. V_T was slightly higher in hyperoxemic patients, and the difference in PEEP persisted over the successive days (Fig. 2, eTable 2 and eFigure 3). Rescue therapies for hypoxemia were applied more often in normoxemic patients (Table 2 and eTable 2).

Outcomes

A flat relationship was seen between 28−day mortality and PaO_2 at day 1; a U−shape relationship was seen between

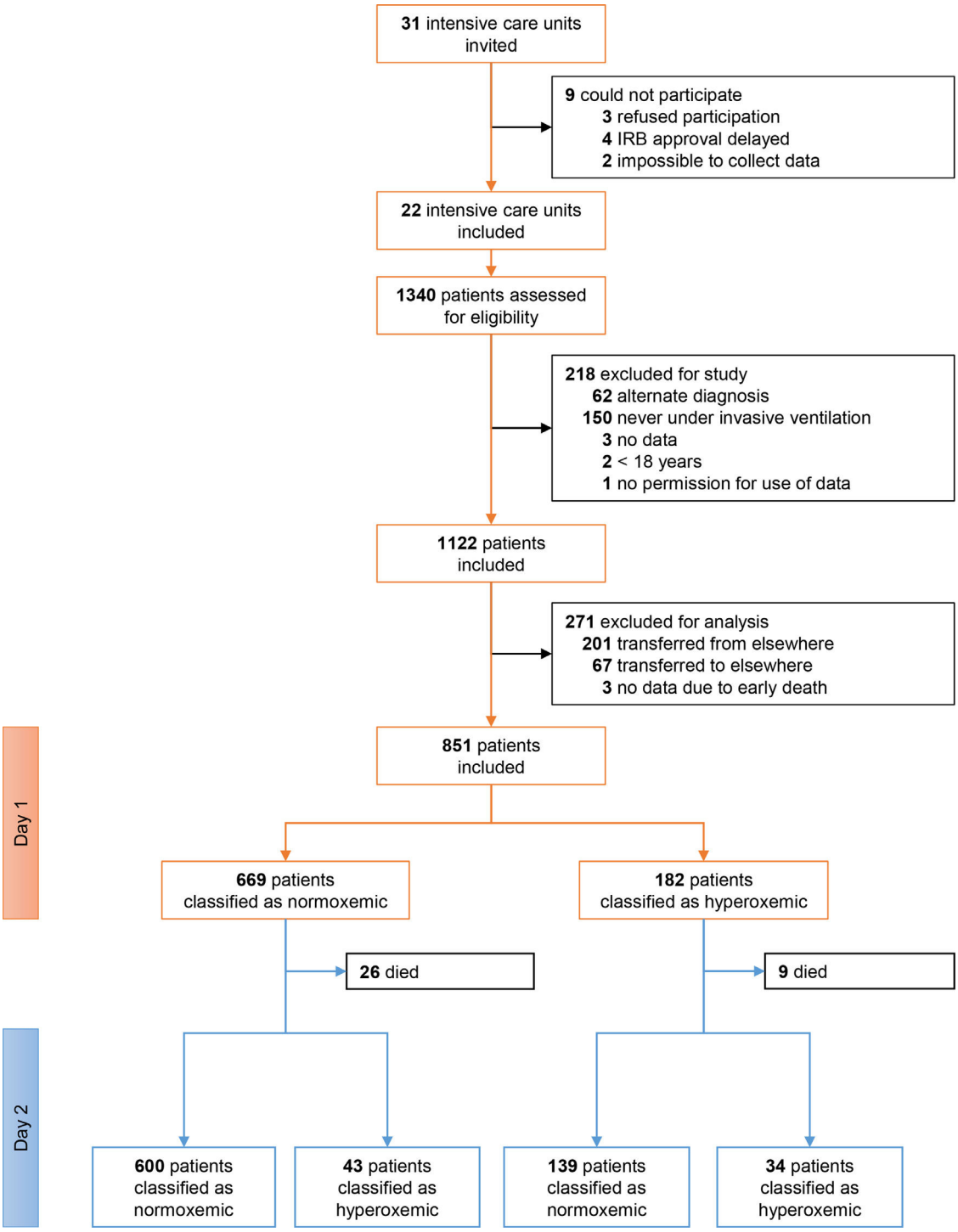

Fig. 1 Flowchart of inclusions.

28–day mortality and PaO_2 at day 2, with a nadir PaO_2 of 75 mmHg (eFigure 4). Mortality rates increased with higher FiO_2 (eFigure 5).

Duration of ventilation and length of stay in hospital and ICU were shorter in hyperoxemic patients (Table 2), but not when death was treated as a competing risk (Fig. 3, eFigure 6 and 7). Mortality was not different between the two groups (Table 2, eFigure 8 and 9).

Matched analysis

We matched 346 patients, resulting in fairly comparable groups, with persisting differences in PaO_2 (Table 1, eTable 1 and 3, and eFigure 1, **10** and **11**). In the matched analysis, there were no differences in any of the clinical outcomes (Table 2, Fig. 3, eFigures 6 to 9).

Table 1 Baseline Characteristics of the Patients According to the Groups In the Unmatched and Matched Cohort.

	Unmatched Cohort (n = 851)			Matched Cohort (n = 346)		
	Hyperoxemic (n = 225)	Normoxemic (n = 626)	p	Hyperoxemic (n = 173)	Normoxemic (n = 173)	p
Age, years	67.0 (58.0–73.0)	65.0 (58.0–72.0)	0.315	67.0 (59.0–73.0)	66.0 (59.0–73.0)	0.763
Male gender–no (%)	157 (69.8)	462 (73.8)	0.257	125 (72.3)	126 (72.8)	0.999
Body mass index, kg/m^2	27.7 (25.5–30.5)	27.8 (25.4–30.8)	0.606	27.7 (25.4–30.7)	27.5 (24.9–30.4)	0.711
Use of non-invasive ventilation–no (%)	17 (7.8)	58 (9.5)	0.495	11 (6.6)	20 (11.6)	0.132
Duration of non-invasive ventilation, hours	4.0 (2.0–11.0)	8.0 (2.0–21.0)	0.320	3.0 (1.5–14.0)	13.0 (2.5–36.0)	0.214
Chest CT scan performed–no (%)	82 (36.4)	224 (35.8)	0.872	55 (31.8)	62 (35.8)	0.495
Lung parenchyma affected–no (%)			0.693			0.042
0%	3 (3.6)	8 (3.5)		0 (0.0)	2 (3.2)	
25%	24 (28.9)	74 (32.7)		15 (26.8)	19 (30.2)	
50%	22 (26.5)	71 (31.4)		14 (25.0)	26 (41.3)	
75%	28 (33.7)	61 (27.0)		22 (39.3)	15 (23.8)	
100%	6 (7.2)	12 (5.3)		5 (8.9)	1 (1.6)	
Chest X-ray performed–no (%)	136 (91.9)	366 (90.4)	0.740	111 (91.7)	102 (91.1)	0.999
Quadrants affected–no (%)			0.306			0.152
1	6 (4.4)	29 (7.9)		5 (4.5)	8 (7.9)	
2	27 (20.0)	90 (24.7)		22 (20.0)	25 (24.8)	
3	41 (30.4)	94 (25.8)		35 (31.8)	19 (18.8)	
4	61 (45.2)	152 (41.6)		48 (43.6)	49 (48.5)	
Severity of ARDS–no (%)			<0.001			0.753
Mild	61 (30.3)	50 (9.1)		29 (18.8)	34 (22.2)	
Moderate	103 (51.5)	317 (57.5)		92 (59.7)	86 (56.2)	
Severe	36 (18.0)	184 (33.4)		33 (21.4)	33 (21.6)	
Co-existing disorders–no (%)						
Hypertension	72 (32.0)	210 (33.5)	0.741	64 (37.0)	62 (35.8)	0.911
Heart failure	12 (5.3)	24 (3.8)	0.338	10 (5.8)	7 (4.0)	0.620
Diabetes	42 (18.7)	153 (24.4)	0.080	36 (20.8)	33 (19.1)	0.788
Chronic kidney disease	7 (3.1)	28 (4.5)	0.439	5 (2.9)	2 (1.2)	0.448
Baseline creatinine, μmol/L*	77.0 (64.0–96.2)	76.0 (61.0–96.0)	0.263	80.0 (65.0–98.0)	74.5 (61.0–96.0)	0.153
Liver cirrhosis	1 (0.4)	2 (0.3)	0.999	0 (0.0)	0 (0.0)	NA
Chronic obstructive pulmonary disease	17 (7.6)	52 (8.3)	0.778	14 (8.1)	15 (8.7)	0.999
Active hematological neoplasia	5 (2.2)	9 (1.4)	0.540	2 (1.2)	2 (1.2)	0.999
Active solid neoplasia	8 (3.6)	13 (2.1)	0.218	6 (3.5)	2 (1.2)	0.283
Neuromuscular disease	1 (0.4)	5 (0.8)	0.999	1 (0.6)	0 (0.0)	0.999
Immunosuppression	8 (3.6)	14 (2.2)	0.327	4 (2.3)	5 (2.9)	0.999
Previous medication–no (%)						
Systemic steroids	11 (4.9)	24 (3.8)	0.557	9 (5.2)	10 (5.8)	0.999
Inhalation steroids	29 (12.9)	70 (11.2)	0.544	21 (12.1)	24 (13.9)	0.750
Angiotensin converting enzyme inhibitor	45 (20.0)	107 (17.1)	0.361	38 (22.0)	37 (21.4)	0.999
Angiotensin II receptor blocker	29 (12.9)	65 (10.4)	0.322	23 (13.3)	23 (13.3)	0.999
Beta-blockers	45 (20.0)	124 (19.8)	0.999	37 (21.4)	32 (18.5)	0.591
Insulin	13 (5.8)	46 (7.3)	0.540	9 (5.2)	10 (5.8)	0.999
Metformin	31 (13.8)	107 (17.1)	0.292	26 (15.0)	27 (15.6)	0.999

Table 1 (*Continued*)

	Unmatched Cohort (*n* = 851)			Matched Cohort (*n* = 346)		
	Hyperoxemic (*n* = 225)	Normoxemic (*n* = 626)	*p*	Hyperoxemic (*n* = 173)	Normoxemic (*n* = 173)	*p*
Statins	72 (32.0)	196 (31.3)	0.867	59 (34.1)	55 (31.8)	0.732
Calcium channel blockers	33 (14.7)	117 (18.7)	0.186	30 (17.3)	35 (20.2)	0.582
Vital signs						
Heart rate, bpm	91.0 (78.5–104.0)	92.0 (79.0–107.0)	0.480	91.0 (79.5–104.0)	90.0 (78.0–105.0)	0.890
Mean arterial pressure, mmHg	85.0 (73.0–99.5)	86.0 (75.0–102.0)	0.531	86.0 (75.8–100.3)	83.0 (72.0–99.0)	0.176
Organ support–no (%)						
Continuous sedation	214 (95.1)	605 (97.0)	0.209	163 (94.2)	168 (97.7)	0.171
Inotropic or vasopressor	184 (81.8)	484 (77.6)	0.217	139 (80.3)	142 (82.6)	0.678
Vasopressor	183 (81.3)	484 (77.6)	0.256	138 (79.8)	142 (82.6)	0.582
Inotropic	13 (5.8)	22 (3.5)	0.170	11 (6.4)	9 (5.2)	0.818
Fluid balance, mL	739.0 (124.2–1528.0)	634.0 (17.4–1427.7)	0.113	759.0 (112.0–1573.5)	716.0 (104.0–1555.0)	0.798
Urine output, mL	698.5 (352.5–1090.0)	760.0 (420.0–1215.0)	0.032	655.0 (350.0–1055.0)	750.0 (395.0–1165.0)	0.163

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding.

Sensitivity analysis

The sensitivity analysis in which we excluded hypoxemic patients did not show differences in clinical outcomes (eTable 4 and 5; eFigure 12 to 14).

Discussion

In this cohort of intubated patients with COVID–19 ARDS (1) the prevalence of hyperoxemia was high, and (2) many patients experienced excessive oxygen use, albeit that the

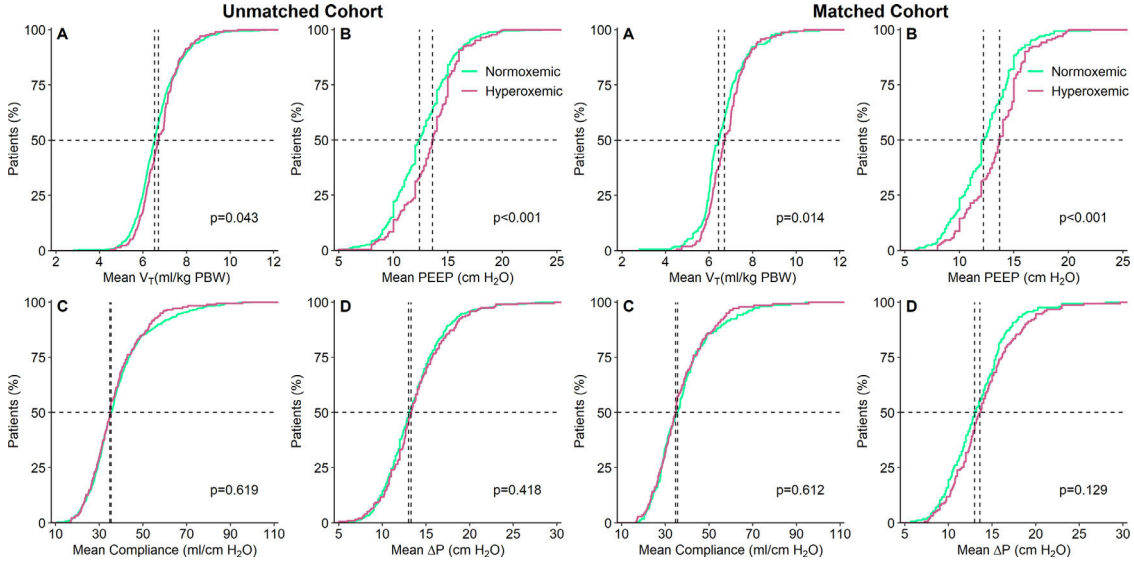

Fig. 2 Cumulative frequency distributions of ventilation variables on day 1 of ventilation in the hyperoxemic (purple) and normoxemic (green) group, in the unmatched (left panels) and matched (right panels) cohorts. Horizontal dotted lines represent 50% of the patients and vertical dotted lines represent the median of the variable at the start of ventilation. All measurements are the means of a maximum of six measurements. P–values from Wilcoxon–Mann–Whitney test.
V_T: tidal volume; PBW: predicted body weight; MP: mechanical power; VR: ventilator ratio; ΔP: driving pressure, RR: respiratory rate; MV: minute ventilation.

Table 2 Clinical Outcomes According to Groups In the Unmatched and Matched Cohort.

	Unmatched Cohort (n = 851)			Matched Cohort (n = 346)		
	Hyperoxemic (*n* = 225)	Normoxemic (*n* = 626)	*p*	Hyperoxemic (*n* = 173)	Normoxemic (*n* = 173)	*p*
Duration of ventilation, days	12.0 (7.0 – 22.0)	14.0 (8.0 – 23.0)	0.043	12.0 (7.0 – 21.0)	13.0 (8.0 – 22.5)	0.219
In survivors at day 28, days	14.0 (8.0 – 25.0)	16.0 (10.0 – 28.3)	0.178	14.0 (9.0 – 25.0)	17.0 (10.0 – 26.0)	0.514
Tracheostomy – no (%)	38 (17.0)	106 (17.0)	0.999	29 (17.0)	25 (14.5)	0.557
Reintubation – no (%)	27 (12.1)	81 (13.0)	0.815	20 (11.7)	24 (14.0)	0.628
Pneumothorax – no (%)	6 (2.7)	30 (4.8)	0.246	4 (2.3)	10 (5.8)	0.171
Thromboembolic complications – no (%)	61 (27.1)	192 (30.7)	0.350	44 (25.4)	48 (27.7)	0.715
Pulmonary embolism	42 (18.7)	153 (24.4)	0.080	32 (18.5)	42 (24.3)	0.238
Deep vein thrombosis	10 (4.4)	34 (5.4)	0.726	7 (4.0)	4 (2.3)	0.542
Ischemic stroke	7 (3.1)	19 (3.0)	0.999	5 (2.9)	7 (4.0)	0.770
Myocardial infarction	7 (3.1)	8 (1.3)	0.082	5 (2.9)	2 (1.2)	0.448
Systemic arterial embolism	1 (0.4)	3 (0.5)	0.999	0 (0.0)	1 (0.6)	0.999
Acute kidney injury – no (%)	105 (46.7)	293 (47.1)	0.938	82 (47.4)	83 (48.3)	0.914
Use of RRT – no (%)	43 (19.1)	116 (18.5)	0.842	33 (19.1)	28 (16.2)	0.573
Use of rescue therapy – no (%)*	153 (68.9)	508 (81.5)	<0.001	121 (71.2)	133 (77.3)	0.217
Prone positioning	115 (51.6)	400 (64.2)	0.001	90 (52.6)	96 (55.8)	0.589
Recruitment maneuver	14 (7.4)	39 (7.8)	0.999	11 (7.6)	10 (7.0)	0.999
Use of NMBA	92 (40.9)	328 (52.4)	0.003	75 (43.4)	90 (52.0)	0.132
ECMO	1 (0.4)	7 (1.1)	0.689	1 (0.6)	1 (0.6)	0.999
Use of continuous sedation – no (%)*	224 (99.6)	622 (99.4)	0.999	172 (99.4)	172 (99.4)	0.999
Use of inotropic or vasopressor – no (%)*	220 (97.8)	590 (94.2)	0.044	168 (97.1)	166 (96.0)	0.770
Use of vasopressor	219 (97.3)	590 (94.2)	0.073	167 (96.5)	166 (96.0)	0.999
Use of inotropic	34 (15.1)	54 (8.6)	0.010	27 (15.6)	20 (11.6)	0.347
ICU length of stay, days	14.0 (8.0 – 24.0)	17.0 (10.0 – 27.0)	0.020	14.0 (8.0 – 24.0)	16.0 (9.3 – 27.8)	0.152
In survivors, days	16.0 (10.0 – 32.5)	19.0 (12.0 – 30.0)	0.214	17.0 (10.0 – 32.8)	19.0 (12.0 – 30.5)	0.642
Hospital length of stay, days	21.0 (12.0 – 32.0)	25.0 (16.0 – 39.0)	0.008	21.0 (12.0 – 31.8)	23.0 (14.0 – 38.0)	0.220
In survivors, days	28.0 (20.0 – 42.0)	32.0 (22.0 – 47.0)	0.041	27.5 (20.0 – 42.0)	32.0 (19.0 – 42.3)	0.702
ICU mortality – no (%)	76 (34.1)	221 (35.6)	0.744	65 (38.0)	64 (37.2)	0.911
Hospital mortality – no (%)	79 (36.4)	224 (37.0)	0.935	66 (39.8)	65 (39.4)	0.999
28-day mortality – no (%)	75 (33.6)	193 (31.0)	0.502	63 (36.8)	56 (32.7)	0.496
90-day mortality – no (%)	80 (37.6)	234 (39.5)	0.624	66 (40.7)	66 (41.5)	0.910

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding.
RRT: renal replacement therapy; NMBA: neuromuscular blocking agent; ECMO: extracorporeal membrane oxygenation.
* assessed in the first four days of ventilation.

prevalence per patient was low; in addition, (3) hyperoxemic patients received ventilation with a slightly higher V_T, higher PEEP but a lower FiO_2; and (4) there were no differences in clinical outcomes between hyperoxemic and normoxemic patients.

This analysis is one of the first to investigate the prevalence of hyperoxemia and excessive use of oxygen in a large cohort of invasively ventilated COVID–19 patients. Granular ventilation data was collected over the first days by investigators that were trained in data collection to ensure good

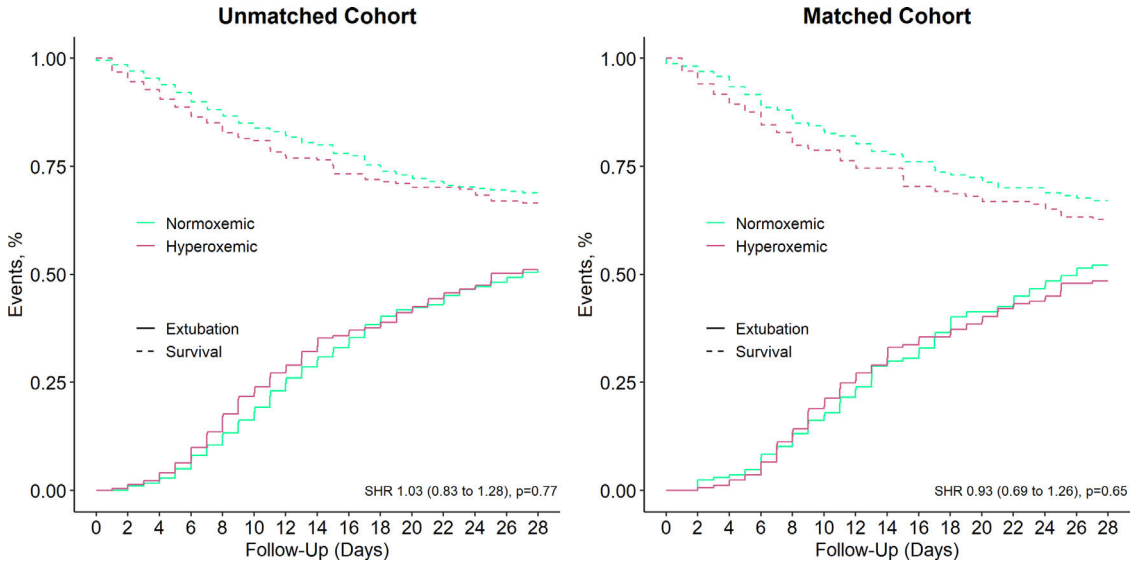

Fig. 3 Mortality and pattern of extubation in the hyperoxemic (pink) and normoxemic (green) groups, before (left panels) and after (right panels) matching. SHR and p−value are from Fine−Gray competing risk model.
SHR: subdistribution hazard ratio.

quality of the data. Patients were included within a relatively short timeframe and therefore unlikely subjected to changes in the local protocols. We recruited patients in different types of hospitals, increasing the generalizability of the findings. This planned analysis was unknown to the caregivers at the time of data collection, minimizing the risk of observation bias. Finally, we had a sophisticated pre−published statistical analysis plan, including a propensity matched analysis to control for confounding factors.

The prevalence of hyperoxemia in our study was comparable,[23,24] but mostly lower[12,25,26] than in other cohorts of COVID−19 patients. One study that specifically examined hyperoxemia in invasively ventilated COVID−19 patients reported a prevalence threefold higher than in our cohort.[26] Patients in that study, alike the other studies that reported a higher prevalence of hyperoxemia under invasive ventilation, had a higher PaO_2/FiO_2 at start of ventilation, suggesting that patients in those studies had less severe ARDS. It cannot be excluded, however, that the caregivers involved in care for patients in our cohort targeted lower oxygen levels, either because of the local protocols that were being used, or because they are more aware of the potential risks of hyperoxemia.[27-29]

The prevalence of hyperoxemia was remarkably lower than that seen in a large international cohort of ARDS patients from 2014.[22] This difference may be explained in several ways. First, it is possible that ventilation strategies have changed over recent years. Lower tidal volumes are increasingly used, and V_T reduction can result in lower oxygen levels, as also seen in the seminal ARDS Network trial named 'ARMA'.[30] Second, and in line with the suggestion above on oxygen targets, the findings of several studies in this topic[5,29,31] may have resulted in lower oxygen targets. Third, hyperoxemia could be more difficult to achieve in patients with COVID−19 ARDS, due to extensive pulmonary infiltrates or sometimes the presence of pulmonary embolism.

One important finding of our study is that outcomes were not different between hyperoxemic versus normoxemic patients. However, this may not be too surprising since the differences in oxygen levels between the two patient groups were not as large as in the initial investigations that studied the effects of hyperoxemia in critically ill patients−−of note, this was also the case in the recent randomized clinical trials that all showed no benefit of a low oxygen versus a high oxygen strategy.[8-11] However, we noted an increasing mortality beyond a PaO_2 of 75 mmHg in the LOESS curve.

Differences in ventilation between hyperoxemic and normoxemic patients were minimal. PEEP, however, was consistently higher in the hyperoxemic patients, even after matching. This may not be unexpected, as higher PEEP can result in more lung recruitment and thus improve oxygenation, as for instance also seen in patients in one study that was performed before just before the COVID−19 pandemic.[32] Alike in patients with ARDS due to another cause, PEEP can also reaerate consolidated regions of the lungs in COVID−19 patients,[33] thereby improving oxygenation.[34] However, we do not suggest that high PEEP should be applied in all COVID−19 patients to improve oxygenation, as improved oxygenation does not automatically result in better outcome and non−recruitable patients are at high risk of overdistension and hemodynamic impairment.[32] Interestingly, prone positioning was used more often in the normoxemic group. This finding suggests that prone positioning was adequately used as a rescue therapy for refractory hypoxemia.

Excessive oxygen use was seen in almost half of the patients in this cohort. However, only 13.6% of all the observed time−points showed excessive use of oxygen, which at least suggests that clinicians responded adequately to hyperoxemia with a reduction in FiO_2. Interestingly, use of excessive oxygen was much lower than in previous cohorts of patients with ARDS due to another cause.[22,27,35] Of note, the LOESS curve demonstrated increasing mortality with increasing levels of FiO_2 regardless of the presence of hyperoxemia, and although this is partially linked to severity of disease, it could also represent the deleterious effects that high levels of FiO_2 can have on lung tissue.[36]

Limitations of this analysis are as follows. We restricted the analysis to the first two days of oxygenation, and therefore cannot be sure whether dysoxemia at later time points had detrimental effects. The definitions of hyperoxemia and excessive oxygen were arbitrary, as there are no definitive targets for PaO_2 or FiO_2. Higher cut-offs for PaO_2 and FiO_2 could have resulted in other prevalences of hyperoxemia and excessive oxygen use, and maybe even associations of dysoxemia with outcome. Due to the low number of hypoxemic patients in this cohort, we were not able to compare outcomes in these patients. However, the sensitivity analysis in which we excluded hypoxemic patients showed that there were no differences in clinical outcomes. We were not able to collect data to gain insight in oxygen management per se, and we did also not collect the protocols in place at the participating centres. Unfortunately, we did not acquire ventilation data before intubation and therefore were not able to calculate the ROX index in patients previously on high flow nasal oxygen (HFNO). This index (ratio of SpO_2/FiO_2 to respiratory rate (RR)) predicts whether patients on HFNO will be in need of intubation, and it would have been interesting to see whether hyperoxemic patients had a lower chance of HFNO failure based on the ROX index.

Conclusions

In this cohort of COVID−19 ARDS patients, hyperoxemia and excessive oxygen use occurred often, but prevalences were lower than in previous studies in patients with ARDS due to another cause. The main difference between hyperoxemic and normoxemic patients was ARDS severity, use of PEEP and FiO_2 and prone positioning. We found no effect of hyperoxemia on outcomes.

Conflicts of interest

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2022.09.003.

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