Classification and effectiveness of different oxygenation goals in mechanically ventilated critically ill patients: network meta-analysis of randomised controlled trials

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Shareable abstract (@ERSpublications)
The available evidence does not suggest different effects on mortality among different oxygenation goals in mechanically ventilated critically ill patients. The P_{aO_2} range of 70–150 mmHg is potentially superior but remains to be validated. https://bit.ly/3qtMc1D

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Abstract

Background The optimal oxygenation in mechanically ventilated critically ill patients remains unclear.

Methods We performed a systematic review of randomised controlled trials (RCTs) with the aim to classify oxygenation goals and investigate their relative effectiveness. RCTs investigating different oxygenation goal-directed mechanical ventilation in critically ill adult patients were eligible for the analysis. The trinary classification classified oxygenation goals into conservative (partial pressure of arterial oxygen (P_{aO_2}) 55–90 mmHg), moderate (P_{aO_2} 90–150 mmHg) and liberal (P_{aO_2} >150 mmHg). The quadruple classification further divided the conservative goal from the trinary classification into far-conservative (P_{aO_2} 55–70 mmHg) and conservative (P_{aO_2} 70–90 mmHg) goals. The primary outcome was 30-day mortality. The secondary outcomes included intensive care unit, hospital and 90-day mortalities. The effectiveness was estimated by the relative risk and 95% credible interval (CrI) using network meta-analysis and visualised using surface under the cumulative ranking curve (SUCRA) scores and survival curves.

Results We identified eight eligible studies involving 2532 patients. There were no differences between conservative and moderate goals (relative risk 1.08, 95% CrI 0.85–1.36; moderate quality), between moderate and liberal goals (relative risk 0.83, 95% CrI 0.61–1.10; low quality) or between conservative and liberal goals (relative risk 0.89, 95% CrI 0.61–1.30; low quality) based on the trinary classification. There were no differences in secondary outcomes among the different goals. The results were consistent between the trinary and quadruple classifications. The SUCRA scores and survival curves suggested that the moderate goal in the trinary and quadruple classifications and the conservative goal in the quadruple classification may be superior to the liberal and far-conservative goals.

Conclusions Different oxygenation goals do not lead to different mortalities in mechanically ventilated critically ill patients. The potential superiority of maintaining P_{aO_2} in the range 70–150 mmHg remains to be validated.

Introduction

Mechanical ventilation in an intensive care unit (ICU) is associated with mortality rates up to 30–50%, depending on the aetiology and severity of the disease [1, 2]. Endeavours to improve survival in mechanically ventilated patients are thus of paramount importance. Among the multiple potential causes of these poor outcomes, inappropriate goals of arterial blood oxygenation used during the management of mechanical ventilation may play a role [3].

Multiple randomised controlled trials (RCTs) have been performed to compare the relative effectiveness between different oxygenation goals in mechanically ventilated critically ill patients. GIRARDIS *et al.* [4] compared the goal of maintaining partial pressure of arterial oxygen (P_{aO_2}) at 70–100 mmHg and pulse oxygen saturation (S_{pO_2}) at 94–98% with the goal of maintaining P_{aO_2} up to 150 mmHg and S_{pO_2} at 97–100%. They showed that the lower oxygenation goal was associated with a lower ICU mortality (11.6% *versus* 20.2%). In comparison, BARROT *et al.* [5] compared the goal of maintaining P_{aO_2} at 55–70 mmHg and S_{pO_2} at 88–92% with the goal of maintaining P_{aO_2} at 90–105 mmHg and S_{pO_2} ⩾96%. They found that the lower oxygenation goal was associated with a higher ICU mortality (36.4% *versus* 26.5%). Not only are these results contrasting, but the goals used by these two studies were also different. While the higher oxygenation goals utilised by these two studies were similar, the lower oxygenation goals were P_{aO_2} 70–100 mmHg [4] and 55–70 mmHg [5], respectively, which do not even overlap. These two studies highlight the importance of standardising oxygenation goals for the purposes of both research and clinical practice.

A recent systematic review concluded that in acutely ill adults, liberal oxygen therapy increases mortality and supplemental oxygen might become unfavourable if S_{pO_2} is above the range of 94–96% [6]. In contrast, another recent systematic review was unable to draw conclusions on the relative effectiveness between higher and lower fractions of inspired oxygen (F_{IO_2}) or targets of arterial oxygenation in adult ICU patients [7]. Due to the heterogeneity in patient characteristics, methods of oxygen therapy and intervention end-points, it is difficult to interpret the results of these systematic reviews with pairwise meta-analysis. To date, there is no network meta-analysis investigating the effectiveness of different oxygen therapies.

It is our hypothesis that there is an optimal goal of arterial blood oxygenation in mechanically ventilated critically ill patients. The aims of this systematic review of RCTs are to classify oxygenation goals and investigate their relative effectiveness in terms of mortalities in mechanically ventilated ICU patients using network meta-analyses and the surface under the cumulative ranking curve (SUCRA).

Methods

Protocol and registration

We designed and wrote the study according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions (PRISMA-NMA) guidelines [8]. The study was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020180392).

Eligibility criteria

RCTs comparing the relative effectiveness between different oxygenation goals in mechanically ventilated critically ill patients were eligible. The inclusion criteria included 1) adult patients (⩾18 years old); 2) ICU setting; 3) >50% of study participants received mechanical ventilation; 3) comparison between different oxygenation goals defined by P_{aO_2}, arterial oxygen saturation (S_{aO_2}) or S_{pO_2}; 4) mechanical ventilation management guided by different oxygenation goals for at least 24 h; 5) actual oxygenation levels reported; and 6) mortality reported. We considered studies which, although comparing different F_{IO_2} management methods, reported the actual oxygenation levels. We excluded studies that were performed intra-operatively on surgical patients or during the resuscitation of cardiopulmonary arrested patients. The primary outcome was 30-day (including 28-day) mortality. The secondary outcomes included ICU, hospital and 90-day mortalities. There were no restrictions on publication year or language. Both full-text articles and abstracts were eligible.

Information sources and search

We systematically searched Ovid MEDLINE, Ovid Embase, Web of Science and the Cochrane database from inception to 17 April 2020 (search strategy included in the supplementary material). The reference lists of all relevant articles were manually screened to supplement the systematic search.

Study selection and data collection

We used EndNote version 8.0 (Clarivate, Philadelphia, PA, USA) for study deduplication and selection. Two investigators (X.Z. and H.X.) independently screened all deduplicated titles and abstracts derived from the systematic search, evaluated the full candidate articles to determine their eligibility, and performed data extraction using a predesigned data form. Between-investigator disagreements were resolved *via* team discussion.

Data items

The data items extracted from each eligible study were: 1) authors and year of publication; 2) study design, patient characteristics and number of patients receiving mechanical ventilation; 3) goals of oxygenation defined by the protocol and the actual oxygenation levels; and 4) outcome measures and results.

Risk of bias of individual studies

The Cochrane Collaboration's tool was used to assess the risk of bias in each study [9]. A study was rated as having a high risk of bias overall if one or more domains were rated as having a high risk of bias. A study was rated as having an unclear risk of bias overall if one or more domains were rated as having an unclear risk of bias while the other domains were rated as having a low risk of bias. Otherwise, a study was rated as having a low risk of bias.

Network geometry

We constructed network geometries to visualise the comparisons between the different oxygenation goals. The oxygenation goals were classified per the following trinary classification system: 1) conservative (defined as P_{aO_2} 55–90 mmHg and S_{aO_2}/S_{pO_2} 88–97%), 2) moderate (defined as P_{aO_2} 90–150 mmHg and S_{aO_2}/S_{pO_2} 97–100%) and 3) liberal (defined as P_{aO_2} >150 mmHg) (figure 1a). Accordingly, the network geometry had three nodes corresponding to the different oxygenation goals. We used the actual oxygenation level, instead of the targeted oxygenation level, to determine the oxygenation goal's class for each randomisation group of individual studies. Each randomisation group was assigned to a node according to its oxygenation goal classification. The size of the node was determined by the total number of patients. Different nodes were connected by edges, with the size of the edge determined by the total number of direct comparisons.

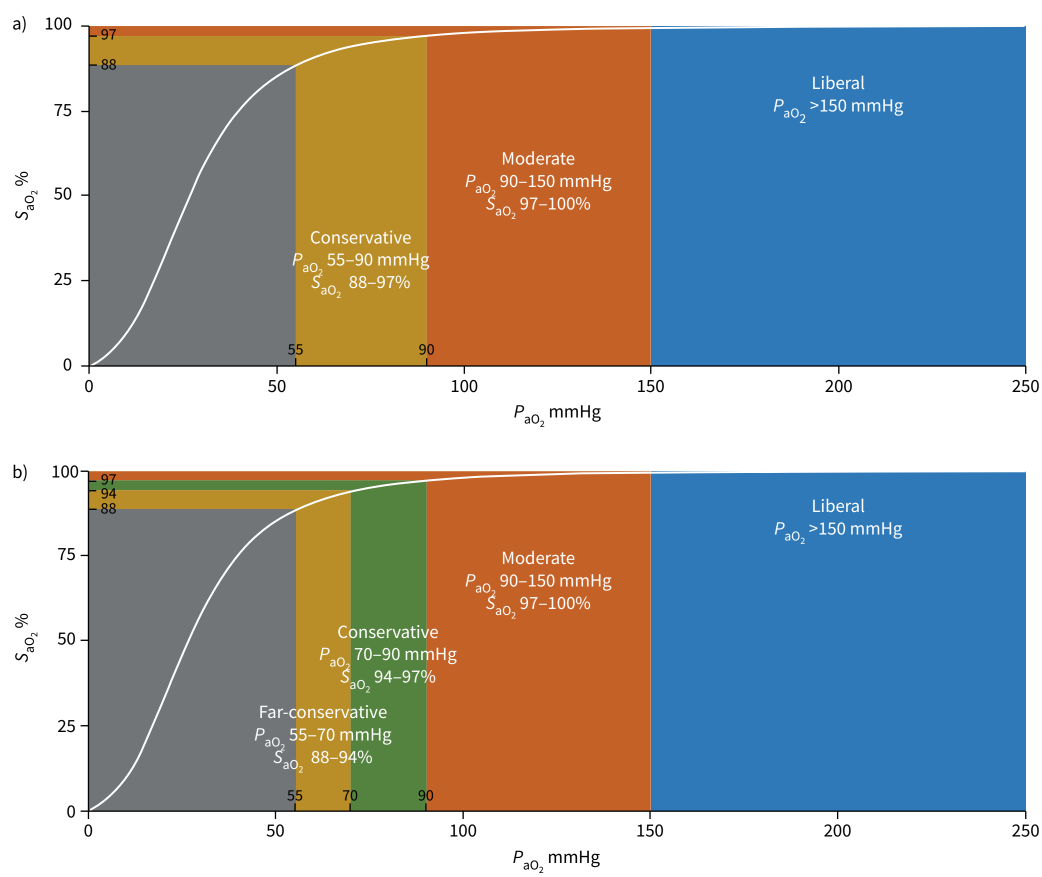

FIGURE 1 Classification of oxygenation goals: a) trinary classification and b) quadruple classification. S_{aO_2}: arterial oxygen saturation; P_{aO_2}: partial pressure of arterial oxygen. The conservative goal in the a) trinary classification is further divided into conservative and far-conservative goals in the b) quadruple classification. The oxyhaemoglobin dissociation curve was based on the equation developed by SEVERINGHAUS [53]: $S_{aO_2}=(23\,400\times(P_{aO_2}{}^{3}+150\times P_{aO_2})^{-1}+1)^{-1}$.

Summary measures

We used the relative risk, 95% confidence interval (CI) and 95% credible interval (CrI) to measure the relative effectiveness between the different oxygenation goals. The efficacy hierarchy was visualised using the SUCRA score, which is a metric used to evaluate which treatment in a network is likely to be the most effective [10].

Planned methods of analysis

For the network meta-analysis, the pooled relative risk for a given comparison was based on direct evidence derived from individual studies and indirect evidence derived from the network. We used a Bayesian hierarchical random effects model with a binomial likelihood and log link function to simulate the probability of events [11]. The pooled estimates were derived using the Markov Chain Monte Carlo method. Three chains of 100 000 iterations were used after a burn-in period of 50 000 iterations, in which initial iterations were discarded to ensure that the final estimates were based on stable posterior sampling. Convergence was assessed using the Brooks–Gelman–Rubin statistic. The network meta-analysis was performed using the R package "gemtc" in R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) [12].

For the pairwise meta-analysis, we used fixed effects models if the total number of studies was less than five and random effects models otherwise using the R package "metafor" [13]. We chose fixed effects models because if fewer than five studies are included in a meta-analysis, the between-study variance cannot be estimated reliably using random effects models [14]. The I^2 statistic was calculated to measure the heterogeneity of the included studies. Trial sequential analysis was used to calculate the required information size to control for type I (false-positive) and type II (false-negative) errors [15]. TSA software version 0.9.5.10 beta (Copenhagen Trial Unit, Copenhagen, Denmark) was used for the trial sequential analysis [16, 17].

Assessment of inconsistency

The node splitting method, separating the evidence for each comparison into direct and indirect evidence, was used to appraise the inconsistency of the results [18].

Publication bias across studies

Funnel plots and Egger's test were used to analyse the potential publication bias for direct comparisons based on three or more studies [19].

Quality of evidence

The quality of evidence for each network estimate was assessed according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) guidelines, which appraise the quality of a body of evidence on the basis of study limitations, imprecision, inconsistency, indirectness and publication bias for the targeted outcome [20].

Additional analysis

We investigated the relative effectiveness of different oxygenation goals using a quadruple classification system, which serves as a sensitivity test for the trinary classification system. The oxygenation goals were classified as 1) far-conservative (defined as P_{aO_2} 55–70 mmHg and S_{aO_2}/S_{pO_2} 88–94%), 2) conservative (defined as P_{aO_2} 70–90 mmHg and S_{aO_2}/S_{pO_2} 94–97%), 3) moderate (defined as P_{aO_2} 90–150 mmHg and S_{aO_2}/S_{pO_2} 97–100%) and 4) liberal (defined as P_{aO_2} >150 mmHg) (figure 1b). This quadruple classification divided the conservative goal (*i.e.* P_{aO_2} 55–90 mmHg) in the trinary classification into far-conservative (*i.e.* P_{aO_2} 55–70 mmHg) and conservative (*i.e.* P_{aO_2} 70–90 mmHg) goals. In the quadruple classification, the far-conservative goal was consistent with the goal used in the RCTs performed by Barrot *et al.* [5] and Panwar *et al.* [21], while the conservative goal was consistent with the goal used by the RCTs performed by Mackle *et al.* [22] and Girardis *et al.* [4].

We performed additional meta-analysis based on the patient-level time-to-event data to corroborate the primary analysis based on the aggregate mortality outcome data, similar to the previous report by Chu *et al.* [6]. The patient-level data were extracted from publications that reported Kaplan–Meier curves using DigitizeIt software (I. Bormann, Braunschweig, Germany) and the algorithm described by Guyot *et al.* [23]. New Kaplan–Meier curves corresponding to the different oxygenation goals defined by the trinary or quadruple classification were constructed using pooled extracted data [24]. The log-rank test was used to compare the survival distributions of these samples. Cox regression models with the study treated as a random effects variable were fitted to compare the effects of different oxygenation goals on mortality, with the relative effectiveness measured by the hazard ratio (HR) with 95% CI.

Results

Study selection

The study selection process and results are detailed in figure 2. We identified eight eligible studies published between 2014 and 2020 [4, 5, 21, 22, 25–28].

Characteristics of individual studies

Of the eligible studies, six were multicentre trials [5, 21, 22, 26–28], while two were single-centre trials (table 1) [4, 25]. One was a feasibility study [27] and three were pilot studies [21, 25, 26]. Three studies were terminated early due to safety concerns [27], safety and futility concerns [5], and earthquake-related slow enrolment [4], respectively. Three studies used 28-day mortality as the primary outcome [5, 25, 28], one study used ICU mortality as the primary outcome [4], while the remaining four studies used a primary outcome that was not a form of mortality [21, 22, 26, 27]. Five studies reported 30-day mortality [5, 22, 25, 26, 28], four studies reported 90-day mortality [5, 21, 22, 28], five studies reported ICU mortality [4, 5, 21, 22, 25] and three studies reported hospital mortality [4, 22, 27] (table 2). Six studies found no between-group difference in mortality [21, 22, 25–28], while one study found reduced ICU and hospital mortalities in patients treated with a lower oxygenation goal [4], and one study found reduced 90-day mortality in patients treated with a higher oxygenation goal [5]. Details of interventions reported by individual studies are presented in supplementary table E1.

Risk of bias of individual studies

The risks of bias of individual studies are presented in supplementary table E2. Four studies had a low risk of bias [5, 21, 22, 26] and four studies had an unclear risk of bias [4, 25, 27, 28]. The pooled risks of bias are presented in supplementary figure E1.

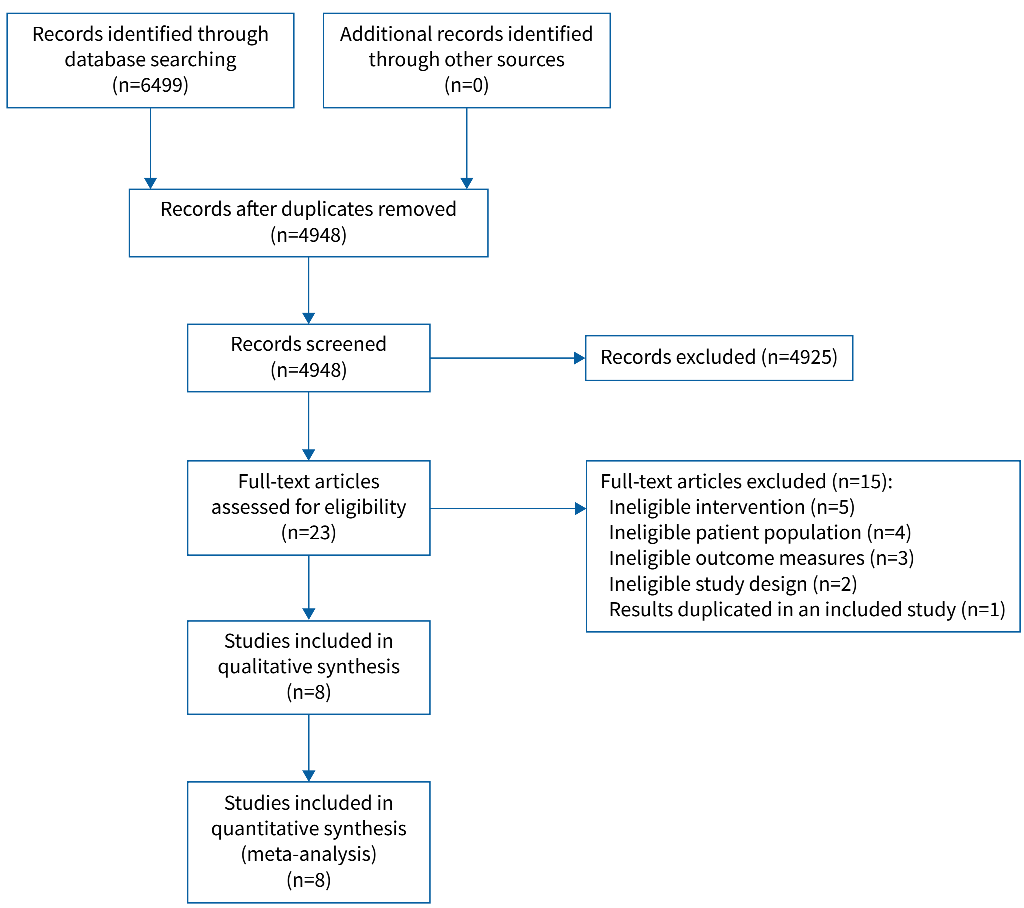

FIGURE 2 Study identification and selection flow diagram.

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TABLE 1 Characteristics of individual studies with oxygenation goals classified

Study	Study design	Patients	Mechanical ventilation %	Targeted oxygenation per protocol[#]		Actual oxygenation per results of individual studies[¶]			
				Lower goal	Higher goal	Lower goal	Classification[+]	Higher goal	Classification[+]
Young *et al.* (2014) [27]	Multicentre feasibility study, early termination	Post-out-of-hospital cardiac arrest (n=17), mean age 66 years, male 94%, P_{aO_2}/F_{IO_2} not reported	100	S_{pO_2} 90–94%, from time of randomisation until 72 h later or extubation	S_{pO_2} >95%, from time of randomisation until 72 h later or extubation	Median (IQR) P_{aO_2} 77 (72–79) mmHg, median (IQR) S_{aO_2} 96% (95–97%), 18 h[§]	Conservative (trinary); conservative (quadruple)	Median (IQR) P_{aO_2} 104 (91–115) mmHg, median (IQR) S_{aO_2} 98% (97–99%), 18 h[§]	Moderate (trinary); moderate (quadruple)
Girardis *et al.* (2016) [4]	Single-centre study, early termination	Diverse ICU patients with shock, respiratory, hepatic and/or renal failure (n=478)[ƒ], median age 64 years, male 57%, P_{aO_2}/F_{IO_2} not reported	67[##]	S_{pO_2} 94–98%, P_{aO_2} 70–100 mmHg, during ICU stay	S_{pO_2} 97–100%, P_{aO_2} up to 150 mmHg, during ICU stay	Median (IQR) P_{aO_2} 87 (79–97) mmHg[¶¶]	Conservative (trinary); conservative (quadruple)	Median (IQR) P_{aO_2} 102 (88–116) mmHg[¶¶]	Moderate (trinary); moderate (quadruple)
Panwar *et al.* (2016) [21]	Multicentre pilot study	Diverse ICU patients with a medical, surgical or trauma diagnosis (n=103), mean age 62 years, male 63%, baseline mean P_{aO_2}/F_{IO_2} 247–248	100	S_{pO_2} 88–92%, >24 h	S_{pO_2} ⩾96%, >24 h	Average S_{pO_2} ∼93%[++]	Conservative (trinary); far-conservative (quadruple)	Average S_{pO_2} ∼97%[++]	Moderate (trinary); moderate (quadruple)
Asfar *et al.* (2017) [28]	Multicentre study, early termination	Septic shock (n=434), mean age 67 years, male 64%, baseline mean P_{aO_2}/F_{IO_2} 220–228	100	F_{IO_2} adjusted to maintain S_{aO_2} 88–95%	F_{IO_2} 100% for 24 h after inclusion, thereafter same F_{IO_2} adjustment as the other group	Mean±SD P_{aO_2} 96±39 mmHg, median (IQR) S_{aO_2} 97% (94–98%), 24 h[§§]	Moderate (trinary); moderate (quadruple)	Mean±SD P_{aO_2} 227±124 mmHg, median (IQR) S_{aO_2} 99% (97–100%), 24 h[§§]	Liberal (trinary); liberal (quadruple)
Jakkula *et al.* (2018) [26]	Multicentre pilot study	Post-out-of-hospital cardiac arrest (n=120), mean age 59 years, male 82%, P_{aO_2}/F_{IO_2} not reported	100	P_{aO_2} 75–112 mmHg, S_{pO_2} 95–98%, for first 36 h in ICU	P_{aO_2} 150–188 mmHg, for first 36 h in ICU	Median (IQR) P_{aO_2} 90 (80–100) mmHg[ƒƒ]	Moderate (trinary); moderate (quadruple)	Median (IQR) P_{aO_2} 160 (140–170) mmHg	Liberal (trinary); liberal (quadruple)
Yang *et al.* (2019) [25]	Single-centre pilot study	Diverse ICU patients with a diagnosis of shock, respiratory or renal failure (n=214), median age 59 years, male 64%, P_{aO_2}/F_{IO_2} not reported	84	S_{pO_2} 90–95%	S_{pO_2} 96–100%	Mean±SD S_{pO_2} 95.7±2.3%, median (IQR) P_{aO_2} 84 (71–99) mmHg[###]	Conservative (trinary); conservative (quadruple)	Mean±SD S_{pO_2} 98.2±1.8%, median (IQR) P_{aO_2} 98 (79–116) mmHg[###]	Moderate (trinary); moderate (quadruple)
Barrot *et al.* (2020) [5]	Multicentre, early termination	ARDS (n=201), mean age 63 years, male 64%, baseline mean P_{aO_2}/F_{IO_2} 117–120	100	S_{pO_2} 88–92%, P_{aO_2} 55–70 mmHg, for 7 days	S_{pO_2} ⩾96%, P_{aO_2} 90–105 mmHg, for 7 days	>50% of patients having P_{aO_2} <70 mmHg, >50% of patients having S_{pO_2} <94%[¶¶¶]	Conservative (trinary); far-conservative (quadruple)	>90% of patients having P_{aO_2} 90–120 mmHg, >50% of patients having S_{pO_2} >97%[¶¶¶]	Moderate (trinary); moderate (quadruple)
Mackle *et al.* (2020) [22]	Multicentre	Diverse ICU patients including post-operative patients and patients with an acute brain disease (n=965), mean age 58 years, male 63%, baseline P_{aO_2}/F_{IO_2} 245–259	100	S_{pO_2} 91–97%	S_{pO_2} ⩾91%	P_{aO_2} 80–90 mmHg[+++]	Conservative (trinary); conservative (quadruple)	P_{aO_2} 90–110 mmHg[+++]	Moderate (trinary); moderate (quadruple)

P_{aO_2}: partial pressure of arterial oxygen; F_{IO_2}: inspired oxygen fraction; S_{pO_2}: peripheral oxygen saturation; IQR: interquartile range; S_{aO_2}: arterial oxygen saturation; ICU: intensive care unit; ARDS: acute respiratory distress syndrome. [#]: goal of oxygenation used by individual studies; [¶]: actual oxygenation accomplished by individual studies; [+]: in the trinary classification the actual oxygenation accomplished by individual studies was classified as conservative (P_{aO_2} 55–90 mmHg or S_{aO_2}/S_{pO_2} 88–97%), moderate (P_{aO_2} 90–150 mmHg or S_{aO_2}/S_{pO_2} 97–100%) and liberal (P_{aO_2} >150 mmHg), whereas the in the quadruple classification the actual oxygenation accomplished by individual studies was classified as far-conservative (P_{aO_2} 55–70 mmHg or S_{aO_2}/S_{pO_2} 88–94%), conservative (P_{aO_2} 70–90 mmHg or S_{aO_2}/S_{pO_2} 94–97%), moderate (P_{aO_2} 90–150 mmHg or S_{aO_2}/S_{pO_2} 97–100%) and liberal (P_{aO_2} >150 mmHg) (in both classifications the oxygenation had to be within the range defined in at least 50% of participants); [§]: based on the overall data presented in table 2 of the study [27]; [ƒ]: based on the intent-to-treat population presented in the supplemental content of the study [4]; [##]: based on the data of the modified intent-to-treat population presented in table 1 of the study [4]; [¶¶]: based on the data presented in eFigure 1 in the supplemental content of the study [4]; [++]: based on the overall data presented in figure 2 of the study [21]; [§§]: based on the overall data presented in table 2 in the supplementary appendix of the study [28]; [ƒƒ]: based on the overall data presented in figure 1b of the study [26]; [###]: based on the data presented in table 2 of the study [25]; [¶¶¶]: based on the overall data presented in figure 2 of the study [5]; [+++]: based on the data presented in figure S2 in the supplementary appendix of the study [22].

TABLE 2 Outcome measures and results of individual studies

Study	Outcome measure	Results		Conclusion by the original study
		Group with a lower goal	Group with a higher goal	
Young *et al.* (2014) [27]	Hospital mortality	4/8 (50)	5/9 (56)	No difference
Girardis *et al.* (2016) [4]	ICU mortality (primary outcome)	27/235 (11)	49/243 (20)	Reduced ICU and hospital mortality with a lower goal
	Hospital mortality	58/235 (25)	80/243 (33)	
Panwar *et al.* (2016) [21]	ICU mortality	13/52 (25)	12/51 (24)	No difference
	90-day mortality	21/52 (40)	19/51 (37)	
Asfar *et al.* (2017) [28]	28-day mortality (primary outcome)	77/217 (35)	93/217 (43)	No difference
	90-day mortality	90/217 (41)	104/217 (48)	
Jakkula *et al.* (2018) [26]	30-day mortality	18/61 (30)	20/59 (34)	No difference
Yang *et al.* (2019) [25]	ICU mortality	21/100 (21)	32/114 (28)	No difference
	28-day mortality (primary outcome)	26/100 (26)	37/114 (32)	
Barrot *et al.* (2020) [5]	ICU mortality	36/99 (36)	27/102 (26)	No difference in 28-day mortality, reduced 90-day mortality with a higher goal
	28-day mortality (primary outcome)	34/99 (34)	27/102 (26)	
	90-day mortality	44/99 (44)	31/102 (30)	
Mackle *et al.* (2020) [22]	ICU mortality#	130/484 (27)	119/481 (25)	No difference
	Hospital mortality#	156/484 (32)	143/481 (30)	
	28-day mortality#	151/484 (31)	138/481 (29)	
	30-day mortality#	154/484 (32)	140/481 (29)	
	90-day mortality	166/479 (35)	156/480 (33)	
	180-day mortality	170/476 (36)	164/475 (35)	

Results are presented as events n/patients n (%). ICU: intensive care unit. #: data obtained from the study investigators.

Patient characteristics

The eight eligible studies involved a total of 2532 ICU patients (ranging from 17 to 965 patients). One study involved patients with septic shock [28], one study involved patients with acute respiratory distress syndrome [5], two studies involved patients suffering from out-of-hospital cardiac arrest [26, 27] and four studies involved patients with diverse critical conditions [4, 21, 22, 25]. The median or mean age of participants was in the range 58–67 years. The range of male participants was 57–94%. The participants in six studies were all mechanically ventilated [5, 21, 22, 26–28], while 67% of the participants in one study [4] and 84% of the participants in another study [25] were mechanically ventilated. Four studies reported baseline P_{aO_2}/F_{IO_2} ratios, ranging from 117 to 259 mmHg [5, 21, 22, 28]. More details of inclusion and exclusion criteria, respiratory diseases, and comorbidities reported by individual studies are presented in supplementary table E1.

Summary of classification

Based on the trinary classification, the conservative goal was investigated by six studies [4, 5, 21, 22, 25, 27], the moderate goal by all eight studies [4, 5, 21, 22, 25–28] and the liberal goal by two studies [26, 28]. Based on the quadruple classification, the far-conservative goal was investigated by two studies [5, 21], the conservative goal by four studies [4, 22, 25, 27], and the moderate and liberal goals by the same studies as the trinary classification [26, 28].

Summary of the network geometry

The five studies that reported 30-day mortality had a total of 10 randomisation groups, which were assigned to three nodes corresponding to the different oxygenation goals (figure 3a). The four studies that reported 90-day mortality had a total of eight randomisation groups, which were assigned to three nodes corresponding to the different oxygenation goals (supplementary figure E2a). We were unable to construct a network geometry for the five studies that reported ICU mortality and for the three studies that reported hospital mortality because these studies only compared the conservative goal with the moderate goal.

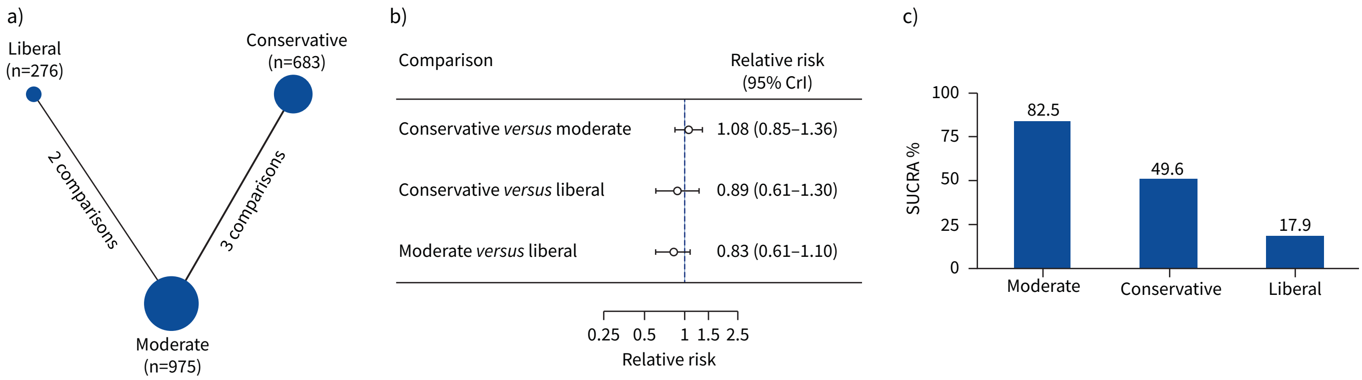

FIGURE 3 Effects of different oxygenation goal-directed mechanical ventilation management methods on 30-day mortality based on the trinary classification: a) network geometry, b) results of network meta-analysis and c) surface under the cumulative ranking curve (SUCRA) scores. CrI: credible interval.

Synthesis of the results

The results based on the trinary classification are presented in table 3, figure 3b and supplementary figure E2b. The 30-day mortality was 31.3% (214 out of 683), 30.7% (299 out of 975) and 40.9% (113 out of 276) for the conservative, moderate and liberal goals, respectively, based on a simple pooling of the data from five studies (table 2). There were no differences between the conservative and moderate goals (relative risk 1.08, 95% CrI 0.85–1.36; moderate quality), between the moderate and liberal goals (relative risk 0.83, 95% CrI 0.61–1.10; low quality) or between the conservative and liberal goals (relative risk 0.89, 95% CrI 0.61–1.30; low quality). The 90-day mortality was 36.7% (231 out of 630), 34.8% (296 out of 850) and 47.9% (104 out of 217) for the conservative, moderate and liberal goals, respectively, based on a simple pooling of the data from four studies (table 2). There were no differences between the conservative and moderate goals (relative risk 1.17, 95% CrI 0.88–1.62; moderate quality), between the moderate and liberal goals (relative risk 0.86, 95% CrI 0.54–1.40; very low quality) or between the conservative and liberal goals (relative risk 1.00, 95% CrI 0.59–1.80; very low quality). There were no differences between the conservative and moderate goals for ICU mortality (relative risk 0.93, 95% CI 0.69–1.26; low quality) and hospital mortality (relative risk 0.97, 95% CI 0.83–1.13; very low quality)

TABLE 3 Estimates of effects and quality of evidence based on the trinary classification

Comparison	Direct evidence[#]		Indirect evidence[¶]		Network meta-analysis[+]	
	Relative risk (95% CI)	Quality	Relative risk (95% CrI)	Quality	Relative risk (95% CrI)	Quality
30-day mortality						
Conservative *versus* moderate	1.07 (0.91–1.26)	Moderate			1.08 (0.85–1.36)	Moderate
Conservative *versus* liberal			0.89 (0.61–1.30)	Low	0.89 (0.61–1.30)	Low
Moderate *versus* liberal	0.83 (0.67–1.04)	Low			0.83 (0.61–1.10)	Low
90-day mortality						
Conservative *versus* moderate	1.13 (0.97–1.31)	Moderate			1.17 (0.88–1.62)	Moderate
Conservative *versus* liberal			1.00 (0.59–1.80)	Very low	1.00 (0.59–1.80)	Very low
Moderate *versus* liberal	0.83 (0.65–1.05)	Very low			0.86 (0.54–1.40)	Very low
ICU mortality						
Conservative *versus* moderate	0.93 (0.69–1.26)	Low				
Hospital mortality						
Conservative *versus* moderate	0.97 (0.83–1.13)	Very low				

CI: confidence interval; CrI: credible interval; ICU: intensive care unit. [#]: direct evidence was based on pairwise meta-analysis which aggregates the results of the head-to-head comparisons between different treatments (quality of direct evidence was assessed per the GRADE guidelines [52], with details of assessment presented in supplementary table E3); [¶]: indirect evidence was based on network meta-analysis which estimates the relative risk between two treatments based on their comparisons with other treatments in the network, but not their direct comparisons (quality of indirect evidence was assessed per the GRADE guidelines for network meta-analysis [20]); [+]: the quality of each network estimate was assessed per the GRADE guidelines for network meta-analysis [20] and it was determined by the quality of direct or indirect evidence whichever was higher.

based on pairwise meta-analysis. The moderate goal was likely the most effective for reducing 30-day mortality (SUCRA 82.5%; figure 3c) and 90-day mortality (SUCRA 83.9%; supplementary figure E2c).

Inconsistency, publication bias across studies and quality of evidence

There was no need to explore the inconsistency because no comparison had both direct and indirect evidence. No publication bias was found (supplementary table E3 and supplementary figure E3). The quality of evidence is presented in table 3 and supplementary table E3.

Results of the additional analyses

The results of the analyses based on the quadruple classification are presented in supplementary figures E4–E7 and supplementary tables E4 and E5. There were no differences among the far-conservative, conservative, moderate and liberal goals for the 30-day, ICU, hospital and 90-day mortalities. The likely most effective goals for 30-day mortality reduction were the moderate (SUCRA 75.2%) and conservative (SUCRA 73.1%) goals. The likely most effective goals for 90-day mortality reduction were the moderate (SUCRA 77.7%) and conservative (SUCRA 59.9%) goals.

Six studies reported Kaplan–Meier curves involving 2351 patients. As per the trinary classification, five studies reported survival data related to conservative goal-directed care [4, 5, 21, 22, 25], six studies reported survival data related to moderate goal-directed care [4, 5, 21, 22, 25, 28] and only one study reported survival data related to liberal goal-directed care [28]. The survival analysis based on the extracted patient-level data from these six studies showed that the different oxygenation goal-directed invasive mechanical ventilation management methods might have different levels of effectiveness in terms of mortality (figure 4a). The conservative and moderate goals, although having comparable effectiveness, might both be superior to the liberal goal for mortality reduction. The survival analysis based on the quadruple classification also suggested that different oxygenation goals might have different levels of effectiveness in terms of mortality, and the conservative and moderate goals might both be superior to the liberal and far-conservative goals (figure 4b).

Because some patients were not intubated in two studies [4, 29], we performed additional analyses excluding these two studies. The results of the analyses with and without these two studies were consistent (supplementary figure E8). The trial sequential analysis showed that the z-curves neither reached the required sample size nor surpassed the O'Brien–Fleming monitoring boundaries, suggesting the false-negative possibility of the results (figure 5).

Discussion

Summary of the evidence

We identified a total of eight eligible RCTs investigating the clinical effectiveness of different oxygenation goal-directed invasive mechanical ventilation management strategies in critically ill adult patients. We used the actual, instead of the targeted, levels of oxygenation to classify the different goals used by the individual studies. The primary analysis was based on the trinary classification system. The quadruple classification system was used in the sensitivity analysis. The network meta-analysis showed that different oxygenation goals did not lead to different mortalities in mechanically ventilated critically ill patients. The negative results may be secondary to the inadequate sample size, as suggested by the trial sequential analysis. The SUCRA ranking suggested that the likely most effective oxygenation goals are the moderate goal (P_{aO_2} 90–150 mmHg) as per the trinary classification and the moderate (P_{aO_2} 90–150 mmHg) and conservative (P_{aO_2} 70–90 mmHg) goals as per the quadruple classification. The survival analysis suggested that the conservative goal based on the quadruple classification and the moderate goal based on the trinary and quadruple classification, although likely comparable, might both be superior to the liberal goal and the far-conservative goal. Our findings should be interpreted with caution because the quality of only two bodies of evidence is moderate while the rest is low and very low.

Comparisons with previous studies

The results of our study are in contrast to a recent systematic review with pairwise meta-analysis of RCTs reported by Chu *et al*. [6]. Their review concluded that there is an increased mortality in acutely ill patients receiving liberal oxygen therapy. However, there are noticeable differences between Chu *et al*.'s [6] review and our study. First, their review included studies that were performed in patients with a diversity of diagnoses, including acute stroke [30–36], acute myocardial infarction [37–42], surgery [43–45], resuscitation [46], septic shock [28], traumatic brain injury [47], post-out-of-hospital cardiac arrest [27] and unspecified critical condition [4, 21]. Most patients with acute stroke or acute myocardial infarction or having surgery do not have hypoxaemia. Patients in a critical condition may or may not have hypoxaemia and may have different severities of hypoxaemia if they are hypoxaemic. Moreover, the patients in most of

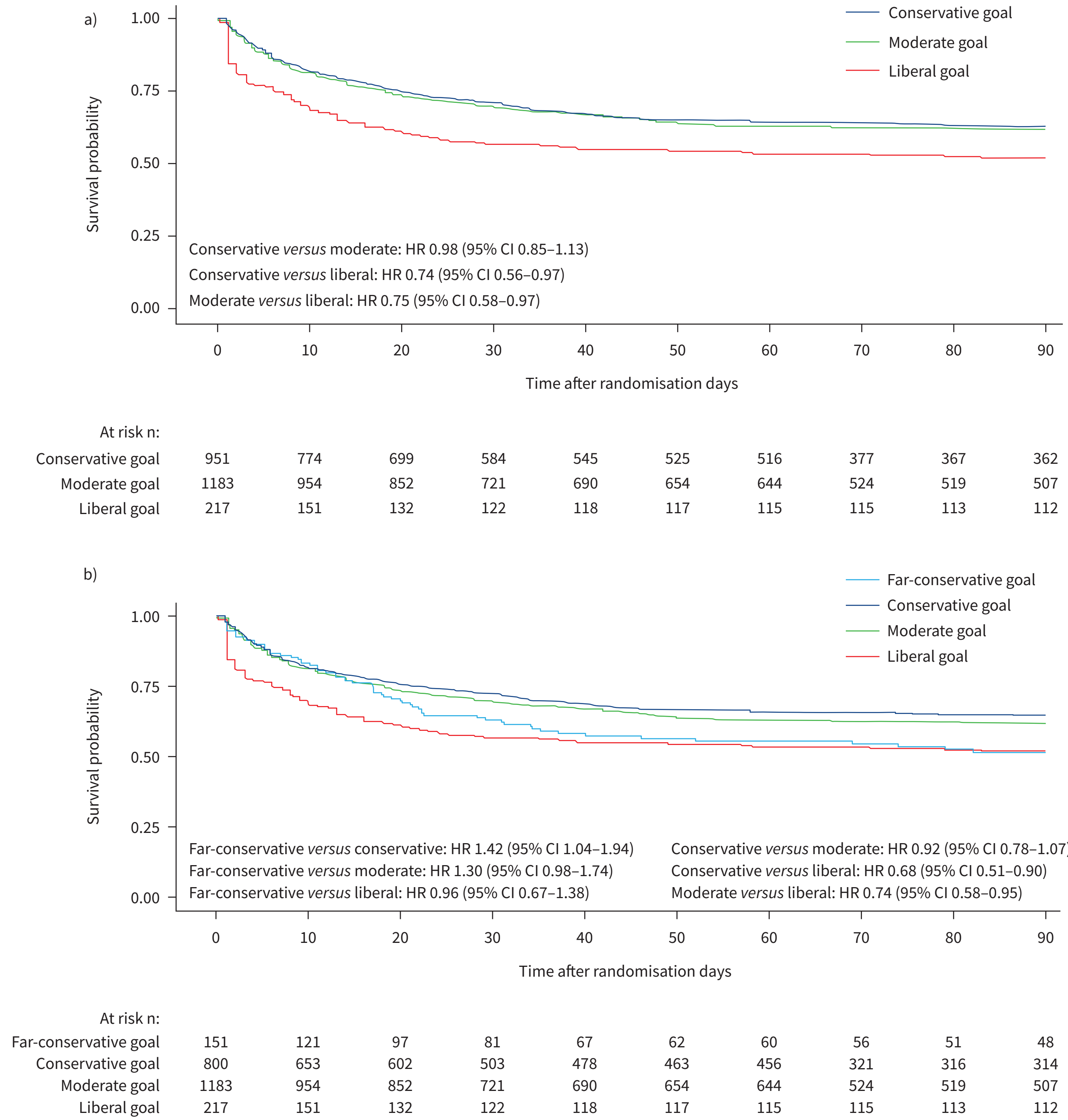

FIGURE 4 Survival probability for patients treated with different oxygenation goal-directed care based on the a) trinary and b) quadruple classifications. HR: hazard ratio; CI: confidence interval. The Kaplan–Meier curves were constructed using the pooled patient-level data extracted from six randomised controlled trials. We used the survival data up to 90 days when available from the following studies: one study up to 28 days [25], one study up to 60 days [4], one study up to 80 days [21] and three studies up to 90 days [5, 22, 28].

the included studies were not endotracheally intubated [30–43], whereas in the rest of the studies they were intubated [4, 21, 27, 28, 44–47]. Second, CHU *et al.*'s [6] review used a binary relative approach to define different oxygen therapies, *i.e.* a treatment targeting a higher F_{IO_2}, P_{aO_2}, S_{aO_2} or S_{pO_2} was defined as liberal oxygen therapy while a treatment targeting a lower value was considered conservative oxygen therapy. The majority of the included studies in their review used F_{IO_2} to differentiate liberal and conservative oxygen

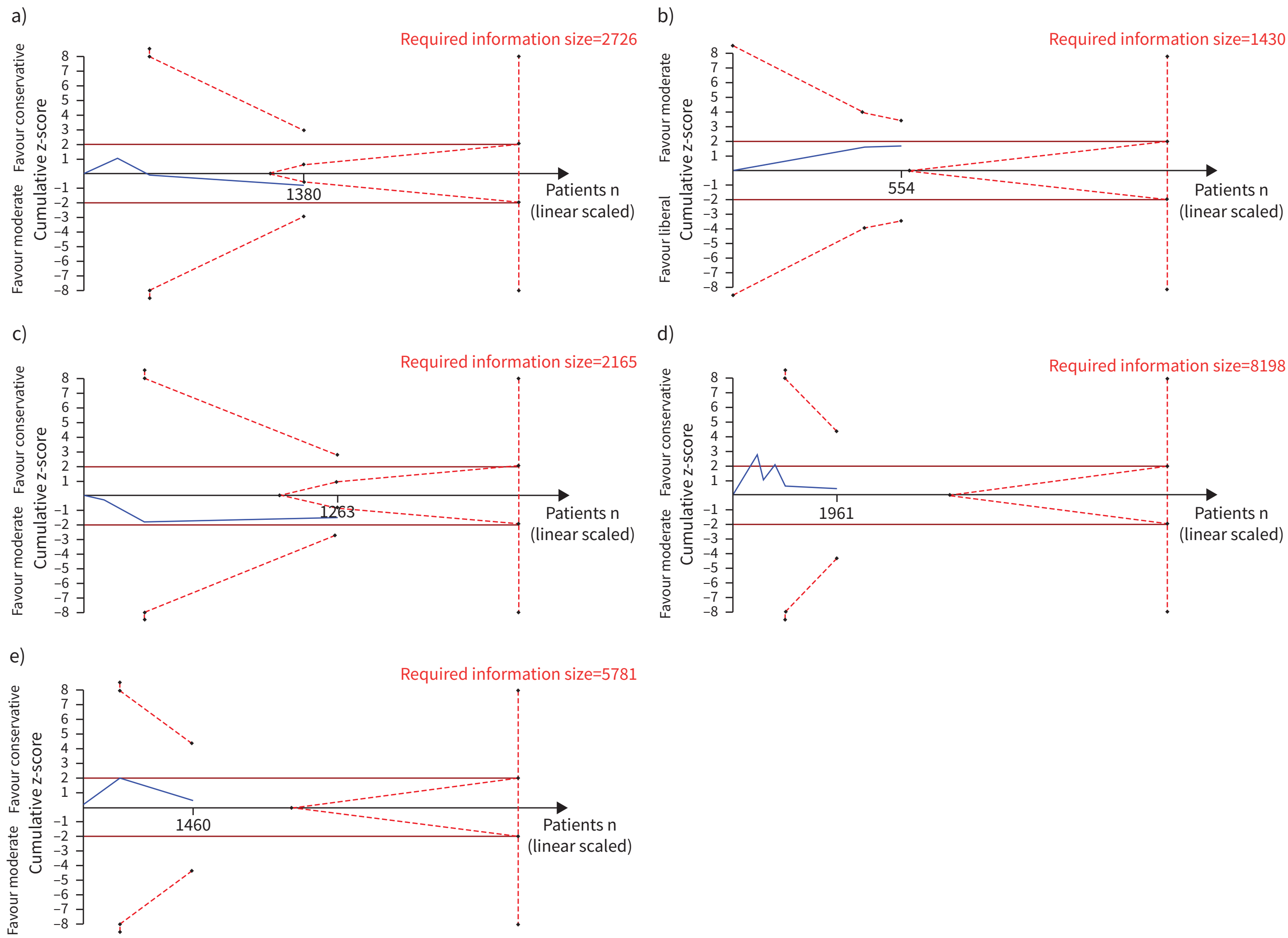

FIGURE 5 Results of trial sequential analysis based on the trinary classification. a) Conservative *versus* moderate goal for 30-day mortality, b) moderate *versus* liberal goal for 30-day mortality, c) conservative *versus* moderate goal for 90-day mortality, d) conservative *versus* moderate goal for intensive care unit mortality and e) conservative *versus* moderate goal for hospital mortality. The abscissa indicates the number of patients (linear scale), while the ordinate indicates the cumulative z-score. The z-score is the test statistic, with a |z| of 1.96 corresponding to a p-value of 0.05, as indicated by the solid brown horizontal lines. A higher z-score corresponds to a lower p-value. The z-curve is indicated by the blue graph line. The red vertical dashed line on the right side indicates the required information size, which was calculated based on the pooled event rates in patients treated by a higher oxygenation goal, two-sided α=0.05, β=0.20 and a 20% relative risk reduction, with adjustments for heterogeneity. The O'Brien–Fleming monitoring boundaries for benefit/harm (top or bottom left-hand corners) and futility (inside the brown horizontal lines) are indicated with red dashed lines.

therapies. The binary relative approach can cause confusion due to the overlap between the different definitions from different studies. For example, one study used F_{IO_2} of 0.30 and 0.21 in the liberal and conservative groups, respectively [30], while another study used F_{IO_2} of 0.80 and 0.30 in the liberal and conservative groups, respectively [44]. Evidently, the F_{IO_2} used in the liberal group in the former study was the same as the F_{IO_2} used in the conservative group in the latter study. Moreover, the studies included in CHU *et al.*'s [6] review used different methods of oxygen delivery, with most studies using either nasal prongs [30, 33, 35, 42] or a face mask [31, 32, 34, 36–41, 43], while the remainder used invasive mechanical ventilation [4, 21, 27, 28, 44–47]. Third, CHU *et al.*'s [6] review did not define or assess the end-points of intervention. The oxygenation goal defined by a prespecified P_{aO_2} or S_{aO_2} value/range should be clarified if the purpose of oxygen therapy is to impact arterial blood oxygenation and not to simply target a specific F_{IO_2}. F_{IO_2} and P_{aO_2} are related but do not follow a linear relationship. How a given change in F_{IO_2} translates into changes in P_{aO_2} is complicated, as exemplified by the concept of the P_{aO_2}/F_{IO_2} ratio that is largely dependent on the severity of the lung disease or gas exchange abnormality. In contrast, our current study only included ICU patients who received oxygenation goal-directed invasive mechanical ventilation, with the oxygenation goal classified by the trinary or quadruple classification system.

An association between a higher oxygenation goal and hazardous effects was suggested by some cohort studies. A large-scale retrospective study found that among patients requiring oxygen therapy, the lowest hospital mortality was observed at S_{pO_2} in the range 94–98% and this finding was consistent across subgroup analyses [48]. A different retrospective study found that P_{aO_2} >120 mmHg was associated with increased ICU mortality [49]. The difficulty of confounding control in cohort studies is one of the major limitations of these studies. In contrast, we only included RCTs in our study. Most importantly, the inclusion in our study of the two RCTs published in 2020 tilted the balance towards a higher oxygenation goal [5, 22]. BARROT *et al*. [5] showed that 28-day mortality was higher in patients treated with a conservative goal (34.3%) than a moderate goal (26.5%). MACKLE *et al*. [22] showed that 30-day mortality was slightly higher in patients treated with a conservative goal (31.8%) than a moderate goal (29.1%) (data shared by the ICU-ROX Investigators). These results are in stark contrast to the results of most studies published before 2020. The chronological discrepancy highlights the complexity of this topic.

The goal of oxygenation

The current oxygenation goal widely adopted for patients with acute respiratory distress syndrome is P_{aO_2} 55–80 mmHg or S_{pO_2} 88–95%. This goal became a well-recognised standard practice following the publication of the ARDSNet ARMA trial in 2000 [50]. However, the study was designed to compare the effectiveness between lower and higher tidal volumes, not to validate the goal of oxygenation *per se*, because both groups in the study targeted the same goal. Nonetheless, the study does illustrate the early attention on the importance of determining the rightful oxygenation goal.

It is highlighted by our study that simply defining an oxygenation goal as higher or lower is not enough. We need to standardise different oxygenation goals using precise terms for the purposes of both research and clinical practice. The trinary and quadruple classifications we propose in this study deserve discussion. First, no matter how hard we try, it is impossible to define the best dividing lines that are in concordance with the criteria used by the different studies. This matter is complicated by the fact that, sometimes, discrepancies exist between the targeted goals and the actual levels. Furthermore, the actual levels seen in a group of patients often follow a wide range of distribution and overlap between groups, especially when the targeted goals have a narrow separation. We chose P_{aO_2} 90 mmHg to divide conservative and moderate goals in the trinary classification because it is not only in concordance with the most recent high-quality study [22], but it is also clinically acceptable to most practitioners. The reason we propose a quadruple classification is to use it as a sensitivity test in case the narrow range defined by P_{aO_2} 70–90 mmHg is more favourable. The reason we primarily used P_{aO_2}, instead of S_{aO_2}, to define different goals was better granularity of P_{aO_2} in differentiating different oxygenation levels at a higher oxygenation range. However, we retained S_{aO_2}/S_{pO_2} in the classification because they are the commonly used parameters in clinical practice.

Despite the discrepancy between our work and the previous work, there is highly likely an optimal range of oxygenation that is associated with the most favourable outcomes. This optimal range is neither too low nor too high; the question remains what this range is. If this range was relatively wide and the goals investigated by some previous studies were within it, this might have caused the failure in detecting a difference in these studies. The quality of most previous studies might also be low, as evidenced by the fact that seven of the eight studies included in our analysis were either pilot studies or were terminated early. Only the study performed by MACKLE *et al*. [22] was regarded as a complete formal study. The currently ongoing Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) trial (ClinicalTrials.gov: NCT03174002) is expected to provide more insights into this topic [51]. At present, it is probably prudent to adopt the P_{aO_2} range 70–150 mmHg in mechanically ventilated critically ill patients based on the overall evidence.

Limitations

Our study has some limitations. First, the trinary and quadruple classifications have not been previously validated, although they are supported by the overall studies and are in concordance with clinical practice. Second, the quality of our meta-analysis might be adversely affected by the quality of the studies included because most of these studies were pilot studies or were terminated early. Third, the lack of studies directly comparing a conservative goal and a liberal goal created a gap in the network we constructed, which may have made our analysis less robust. Fourth, our approach of using the actual instead of the targeted oxygenation levels required judgement based on the data provided by publications. Fifth, our study included critically ill patients with a diversity of diagnoses, which therefore requires caution in generalising our findings. Sixth, the protocols of oxygenation goal-directed invasive mechanical ventilation used by different studies might have varied in ventilation mode, setting, timing and duration, which may have introduced bias into our study.

Conclusions

Our study provides the first network meta-analysis of RCTs investigating the clinical effectiveness between different oxygenation goals in mechanically ventilated critically ill adult patients. Different oxygenation goals did not lead to differences in mortality. However, this negative finding may be secondary to inadequate sample size. The SUCRA ranking and the survival analysis suggested that the moderate goal (P_{aO_2} 90–150 mmHg) based on the trinary and quadruple classifications and the conservative goal (P_{aO_2} 70–90 mmHg) based on the quadruple classification are likely to be the most effective. The inclusion of the two recent RCTs published in 2020 tilted the balance towards the moderate goal. The conflicting evidence calls for further research on this topic. At this time, it may be prudent to maintain P_{aO_2} in the range 70–150 mmHg in mechanically ventilated critically ill patients.

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