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Definition and prognostic value of response to prone positioning in ARDS: a systematic review and meta-analysis

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Abstract

Background Prone positioning improves survival in patients with ARDS; however, no consensus exists on how to define a positive response to this intervention. We conducted a systematic review and meta-analysis to map existing definitions of response to prone position in invasively ventilated patients with ARDS and to quantify their pooled proportion across existing body of evidence. We also evaluated the association between responsiveness to prone position and mortality.

Methods We surveyed PubMed, Embase, and Cochrane Central Register of Controlled Trials databases from inception to July 2025. For the primary outcome (proportion of responders), pooled estimates were calculated using a random-effects model with logit transformation of individual study proportions. For the secondary outcome, we performed a pairwise meta-analysis to estimate pooled odds ratios for mortality.

Results Oxygenation response, defined as a change of PaO_2/FiO_2 from the supine to the prone position, was adopted as definition by 53 non-randomized studies. The pooled proportion of responders was estimated as 68% (95% C.I. 63–72%). Twenty-one studies assessed responsiveness using physiological variables other than, or in addition to, oxygenation, including carbon dioxide clearance, respiratory mechanics, or ventilation–perfusion matching. Using these alternative definitions, the pooled proportion of responders ranged from 45% to 53%. Of the 26 studies providing unadjusted mortality data in responders and non-responders, 11 (42%) reported a reduced risk of mortality in the responder cohort. A sensitivity analysis restricted to the five studies at serious risk of bias showed a reduced unadjusted risk of mortality in responders (OR 0.41, 95% CI 0.25–0.68; $I^2 = 78\%$).

Conclusions Definitions of responsiveness to prone positioning are highly heterogeneous across the literature, and the reported proportion of responders varies widely depending on the definition adopted. High risk of bias, residual confounding and substantial between-study heterogeneity, limit robust conclusions regarding the association between physiological responsiveness to prone positioning and survival.

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Keywords ARDS, Prone position, Mortality, Oxygenation, Respiratory mechanics, Response

Introduction

Prone positioning during invasive mechanical ventilation reduces the risk of mortality in patients with moderate-to-severe Acute Respiratory Distress Syndrome (ARDS) [1, 2]. It reduces mortality, promotes more protective ventilation, improves oxygenation, and enhances CO_2 clearance [3]. Short-term physiological improvements are commonly observed during or immediately after proning and are often interpreted as indicators of treatment efficacy, when these are intermediate, but though sought as mediators, criteria. However, there is no standardised or universally accepted definition of what constitutes a positive "response" to prone positioning [3]. Most studies define response based on oxygenation improvement from supine to prone position (PP), while others consider changes in CO_2 clearance, respiratory mechanics (e.g. driving pressure, compliance), lung imaging, or hemodynamics.

The PROSEVA [2] trial and subsequent randomized trials [3] demonstrated a survival benefit of PP when applied broadly in patients with moderate-to-severe ARDS, regardless of the individual physiological response. Accordingly, efforts to classify response should not aim to guide the decision to initiate PP in patients meeting established severity criteria. Rather, response phenotyping may inform the decision to repeat prone sessions in non-improving patients, identify physiological non-responders who may benefit from alternative or adjunctive rescue strategies, support the titration of duration and frequency of proning across sequential sessions, and enable enrichment in clinical trials. Clinical data show that improved oxygenation does not necessarily translate into reduced ventilator-induced lung injury (VILI) or better outcomes [4], challenging the use of oxygenation-based severity scores [5]. Moreover, these criteria vary substantially in timing (e.g., early vs. late during pronation, or after returning to supine) and methodology, and there is no clear evidence of any association between responsiveness and reduced risk of mortality.

To date, no systematic review has comprehensively examined how "response to prone" is defined and whether it is associated with survival. The aim of this systematic review and meta-analysis was to map the existing definitions and quantify their pooled proportion across existing body of evidence. We also aimed to evaluate the association between responsiveness to PP and mortality in patients with ARDS.

Methods

We conducted a systematic review and meta-analysis of randomized and non-randomized trials investigating the response to PP in patients with ARDS during invasive mechanical ventilation in the ICU.

The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [6] and the study protocol was prospectively registered in the PROSPERO database (Registration number: CRD420251104725).

We surveyed PubMed, Embase, and Cochrane Central Register of Controlled Trials databases from inception to July 2025 using a systematic search strategy combining keywords, MeSH terms or database-specific controlled vocabulary terms, and Boolean operators (see Additional File 1). Further surveillance searches were performed using the 'related articles' feature and snowballing method. Randomized and non-randomized studies evaluating the response rate to prone positioning and/or reporting mortality, grouped by responsive status (i.e. responder vs. non-responder), were included. Case reports, abstracts without full-text availability, conference proceedings, preprint, non-English language reports and studies that did not report the outcomes of interest or do not define a priori responders and non-responders to prone positioning were excluded. Duplicate records were automatically cleaned using Rayyan [7], also adopted as record management platform. Records were screened from titles and abstracts by two authors (A.Ca. and M.I.) blindly. Relevant records were then assessed from full text against the protocolized inclusion and exclusion criteria. Studies were included if the screening authors agreed regarding eligibility. Discrepancies were solved by consensus with a third author (A.Co. or C.G.). The corresponding authors of the screened articles were contacted by two authors (A.Ca., C.G.) when questions arose regarding eligibility or data presentation at any time during this process.

Eligibility criteria and outcomes

For the purpose of our main analysis (i.e. a single-arm meta-analysis on the proportion of responder status), the population (P) was identified as adult patients, defined as aged 18 years or older, with ARDS (including COVID-19) who underwent prone positioning during invasive mechanical ventilation in the ICU; exposure (E) was defined as at least one session of prone positioning, regardless of duration; and outcome (O) was being responders to prone positioning.

Studies were included regardless of the specific ARDS definition applied, provided that authors reported enrolment of patients fulfilling criteria for ARDS according to the contemporaneous definition in use at the time of the study.

Our secondary analysis (i.e. a pairwise meta-analysis on the same population of patients) aimed at evaluating the outcome of mortality in patients with ARDS classified as responders to PP, compared to non-responders.

In both analyses, the patients were classified as responders or non-responders to prone positioning according to criteria predefined by the authors of each included study. Indeed, response to PP could be based on oxygenation (e.g., changes in PaO_2/FiO_2 ratio), respiratory mechanics (e.g., changes in driving pressure or compliance), lung imaging (e.g., improvements on EIT), CO_2 clearance (e.g., changes in $PaCO_2$ or ventilatory ratio) or any other definition adopted by the authors.

The thresholds used to define a response (e.g., absolute or relative changes) were those established by the study authors, based on the criteria reported in each individual study. For the secondary analysis on the outcome of mortality, studies adopting a threshold retrospectively derived from the collected data (e.g. based on median value of PaO_2/FiO_2 of the cohort) were excluded.

Data extraction

Data extraction was performed independently by two authors (A.Ca. and M.I.) using a standardized electronic data collection spreadsheet. Data regarding characteristics of the studies and their population were reported as tables.

Extracted variables included study design, year of publication, country, ARDS etiology, sample size, duration of prone positioning sessions, criteria used to define response, timing of response assessment, use of adjunctive therapies (e.g., ECMO), and reported mortality endpoints.

Risk of bias

Two investigators (A.Ca, M.I.) assessed the risk of bias of the included studies independently and in duplicate. Disagreements over the assessment were resolved by a third author (A.Co.).

The tool by Hoy et al. [8] was used for the assessment of risk of bias for the primary analysis, due to its applicability to prevalence studies and single-arm studies. For the secondary analysis, risk of bias assessment was conducted adopting ROBINS-I V2 tool [9]. It was adopted for both randomized and nonrandomized studies, considering that randomization did not occur for the condition studied by the present analysis (i.e. being responders (E) or non-responders (C)) and all the studies could be considered non-randomized.

Visualization was performed using "*Robvis tool*" [10]. Publication bias for the outcome of mortality was assessed visually using R (Version 2026.01.1–403), package meta, function funnel [11].

Quantitative analysis

A meta-analysis was performed in case of two or more included studies reporting data on the outcomes of interest.

For the primary outcome, proportion of response to PP, pooled estimates were calculated using a random-effects generalized linear mixed model with logit transformation of individual study proportions and are presented with corresponding 95% confidence intervals (C.I.). The analysis was performed in R (Version 2026.01.1–403) using the meta package (function metaprop) [11].

The main analysis was conducted on studies defining response based on oxygenation changes (i.e. PaO_2/FiO_2, from supine to PP). Analyses restricted to studies reporting other definitions of response were also conducted (e.g. oxygenation changes from supine to re-supinated position after PP session, or other definitions).

A subgroup analysis was conducted to investigate the pooled proportion of response to PP defined according to respiratory mechanics, ventilation–perfusion (V/Q) matching or CO_2 clearance. Further analyses, restricted to sub-population, were conducted on studies including only COVID-19 patients, only patients on ECMO, or adopting the Berlin definition for ARDS [12].

For the secondary outcome, we performed a pairwise meta-analysis from raw data comparing mortality in responders and non-responders, providing odds ratios as effect measures. We did not report an overall estimate in cases of critical risk of bias and when combining results was judged not to be appropriate [13]. Heterogeneity was quantified using the I^2 statistic. I^2 values were interpreted as low (< 30%), moderate (30–60%), substantial (50–75%) and considerable (75–100%) heterogeneity [14]. Sensitivity analyses were conducted including only studies at serious overall risk of bias (i.e. excluding studies at critical risk of bias) and only studies providing adjusted estimates of mortality risk.

Calculation of unadjusted pooled estimates was conducted using the inverse variance method and random-effect under the DerSimonian and Laird method, with R (Version 2026.01.1–403), package meta [11], function metabin. Adjusted estimates was calculated using R (Version 2026.01.1–403), package metafor [15], function rma.

Results

Study selection

The search identified 2,570 records from electronic databases and 10 additional records through citation searching from other sources. After removal of 576 duplicates,

Table 1 Characteristics of included studies

Author (year)	Country	Study design	Total patients *n*	Patients proned *n* (%)	COVID19 patients *n* (%)	ECMO PP *n* (%)	Timing of response assessment	Responder definition
Langer M (1988) [37]	Italy	NRSI-P / SC	13	13 (100)	0 (0)	3 (23)*	Immediate-PP	**Oxygenation**: PaO_2 increase ≥ 10 mmHg vs. Supine-Pre-PP
Pappert D (1994) [41]	Germany	NRSI-P / SC	12	12 (100)	0 (0)	NA	Immediate-PP	**Oxygenation**: PaO_2 increase ≥ 10 mmHg vs. Supine-Pre-PP
Vollman KM (1996) [40]	United States	NRSI-P / SC	15	15 (100)	0 (0)	NA	Immediate-PP	**Oxygenation**: PaO_2 increase ≥ 7 mmHg vs. Supine-Pre-PP
Blanch L (1997) [26]	France	NRSI-P / M	23	23 (100)	0 (0)	NA	Early-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 15% vs. Supine-Pre-PP
Chatte G (1997) [33]	United States	NRSI-P / SC	32§	32§ (100)	0 (0)	NA	Immediate-PP / Post-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP **Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg Post-PP vs. Supine-Pre-PP
Jolliet P (1998) [43]	Switzerland	NRSI-P / SC	19	19 (100)	0 (0)	NA	Early-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg or PaO_2 increase ≥ 10 mmHg vs. Supine-Pre-PP
Flaatten H (1998) [35]	Norway	NRSI-P / SC	14	14 (100)	0 (0)	NA	Immediate-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 10% vs. Supine-Pre-PP
Martinez M (1999) [44]	Spain	NRSI-P / SC	14	14 (100)	0 (0)	NA	Early-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20% vs. Supine-Pre-PP
Johannigman JA (2000) [23]	United States	NRSI-P / SC	20	20 (100)	0 (0)	NA	Early-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20% vs. Supine-Pre-PP
Papazian L (2001) [24]	France	NRSI-P / SC	49	49 (100)	0 (0)	NA	Early-PP / Post-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20% vs. Supine-Pre-PP **Oxygenation**: PaO_2/FiO_2 increase ≥ 20% Post-PP vs. Supine-Pre-PP
Lim CM (2001) [25]	Korea (South)	NRSI-P / SC	47	47 (100)	0 (0)	NA	Immediate-PP / Early-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20% vs. Supine-Pre-PP **Oxygenation**: PaO_2/FiO_2 increase ≥ 40% vs. Supine-Pre-PP
Papazian L (2002) [21]	France	NRSI-P / SC	46	46 (100)	0 (0)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 33% vs. Supine-Pre-PP
Lee DL (2002) [34]	Taiwan	NRSI-P / SC	22	22 (100)	0 (0)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP
L'Her E (2002) [20]	France	NRSI-P / SC	51	51 (100)	0 (0)	NA	Immediate-PP / Post-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP **Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg Post-PP vs. Supine-Pre-PP
McAuley DF (2002) [22]	UK	NRSI-P / SC	11	11 (100)	0 (0)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP
Gattinoni L (2003) [31]	Italy and Switzerland	NRSI-P / M	209	209 (100)	0 (0)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP **CO_2clearance**: $PaCO_2$ equal or decreased vs. Supine-Pre-PP
Reutershan J (2004) [19]	Germany	NRSI-P / SC	12	12 (100)	0 (0)	NA	Post-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 30% Post-PP vs. Supine-Pre-PP
Oczenski W (2005) [30]	Austria	NRSI-P / SC	15	15 (100)	0 (0)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20% vs. Supine-Pre-PP
Lemasson S (2006) [16]	France	NRSI-P / M	370	370 (100)	0 (0)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20% vs. Supine-Pre-PP **CO_2clearance**: $PaCO_2$ decreased ≥ 1 mmHg vs. Supine-Pre-PP
Rossetti HB (2006) [45]	Brazil	NRSI-P / SC	41	41 (100)	0 (0)	NA	Immediate-PP / Early-PP / Post-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 15% vs. Supine-Pre-PP **Oxygenation**: PaO_2/FiO_2 increase ≥ 15% Post-PP vs. Supine-Pre-PP
Reutershan J (2006) [18]	Germany	NRSI-P / SC	13	12 (92)	0 (0)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 30% vs. Supine-Pre-PP
Protti A (2009) [27]	Italy and Germany	NRSI-R / M	32	32 (100)	0 (0)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 40 mmHg vs. Supine-Pre-PP **CO_2clearance**: $PaCO_2$ decreased > 0.9 mmHg vs. Supine-Pre-PP
Lee K (2010) [29]	Korea (South)	NRSI-R / SC	96	96 (100)	0 (0)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP **CO_2clearance**: $PaCO_2$ decreased ≥ 1 mmHg vs. Supine-Pre-PP

Table 1 (continued)

Author (year)	Country	Study design	Total patients *n*	Patients proned *n* (%)	COVID19 patients *n* (%)	ECMO PP *n* (%)	Timing of response assessment	Responder definition
Robak O (2011) [28]	Austria	RCT / SC	20	20 (100)	0 (0)	0 (0)	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 10% vs. Supine-Pre-PP
Charron C (2011) [36]	France	NRSI-P / SC	13	13 (100)	0 (0)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP **CO_2clearance**: $PaCO_2$ decreased ≥ 2 mmHg vs. Supine-Pre-PP
Kipping V (2013) [17]	Germany	NRSI-R / SC	12	12 (100)	0 (0)	12 (100)	Post-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20% Post-PP vs. Supine-Pre-PP
Guervilly C (2014) [46]	France	NRSI-P / SC	15	15 (100)	0 (0)	15 (100)	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20% vs. Supine-Pre-PP
Wang XT (2016) [32]	China	NRSI-P / SC	45	45 (100)	0 (0)	0 (0)	Other	**Oxygenation**: PaO_2/FiO_2 ≥300 mmHg at day 7 after initiating PP
Haddam M (2016) [39]	France	NRSI-P / M	51	51 (100)	0 (0)	NA	End-PP / Post-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20% Post-PP vs. Supine-Pre-PP **Oxygenation**: PaO_2/FiO_2 increase > median vs. Supine-Pre-PP **Oxygenation**: PaO_2/FiO_2 increase ≥ 60% Post-PP vs. Supine-Pre-PP **CO_2clearance**: $PaCO_2$ decrease > median Post-PP vs. Supine-Pre-PP
Prat G (2016) [47]	France	NRSI-P / SC	19	19 (100)	0 (0)	1 (5)	Early-PP / End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP
Lee HY (2020) [48]	Korea (South)	NRSI-R / SC	116	116 (100)	0 (0)	0 (0)	End-PP	**Oxygenation**: Increase in PaO_2/FiO_2 ≥53.5% **CO_2clearance**: Increase in VE: $PaCO_2$ ≥41.7%
Dalla Corte F (2020) [49]	Italy	NRSI-P / M	16	16 (100)	0 (0)	NA	Immediate-PP	**Respiratory mechanics**: EIT: improved lung protection = ↑homogeneity (Vtndep/Vtdep →1), ↓ODCL, and ↑ΔEELV vs. Supine-Pre-PP.
Laghlam D (2021) [50]	France	NRSI-P / SC	24	10 (42)	24 (100)	24 (100)	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20% vs. Supine-Pre-PP
Langer T (2021) [51]	Italy	NRSI-R / M	1057	648 (61)$^+$	1057 (100)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP **CO_2clearance**: ΔVR decrease ≥ 0 vs. Supine-Pre-PP
Vollenberg R (2021) [52]	Germany	NRSI-R / M	13	13 (100)	13 (100)	0 (0)	End-PP / Post-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 15% vs. Supine-Pre-PP **CO_2clearance**: $PaCO_2$ decreased ≥ 2% Post-PP vs. Supine-Pre-PP
Weiss TT (2021) [53]	USA	NRSI-R/ SC	42	42 (100)	42 (100)	5 (12)	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20% vs. Supine-Pre-PP
Patel BV (2021) [54]	UK	NRSI-P / M	633	273 (43)	633 (100)	0 (0)	Other	**Oxygenation**: PaO_2/FiO_2 increase ≥ 150 mmHg Post-PP vs. Supine-Pre-PP
Clarke J (2021) [55]	Ireland	NRSI-P / SC	20	20 (100)	20 (100)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20% vs. Supine-Pre-PP
Scaramuzzo G (2021) [56]	Italy	NRSI-P / M	191	191 (100)	191 (100)	3 (1.6)	Post-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 49% Post-PP vs. Supine-Pre-PP
Wang Z (2022) [57]	China	NRSI-R / SC	103	103 (100)	0 (0)	0 (0)	Early-PP / Post-PP	**CO_2clearance**: ΔVR decrease ≥ 0.037 vs. Supine-Pre-PP **Oxygenation**: PaO_2/FiO_2 increase ≥ 22.95 mmHg Post-PP vs. Supine-Pre-PP
Boffi A (2022) [58]	Switzerland	NRSI-R / SC	42	42 (100)	42 (100)	0 (0)	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20% vs. Supine-Pre-PP **CO_2clearance**: $PaCO_2$ decreased ≥ 1 mmHg vs. Supine-Pre-PP
Roy A (2022) [59]	India	NRSI-P / SC	47	47 (100)	47 (100)	NA	End-PP / Post-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20% or PaO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP **Oxygenation**: PaO_2/FiO_2 increase ≥ 20% Post-PP vs. Supine-Pre-PP

Table 1 (continued)

Author (year)	Country	Study design	Total patients *n*	Patients proned *n* (%)	COVID19 patients *n* (%)	ECMO PP *n* (%)	Timing of response assessment	Responder definition
Chen YY (2022) [60]	Taiwan	NRSI-R / SC	96	96 (100)	0 (0)	NA	Early-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20% or PaO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP
Cardinale M (2022) [61]	France	NRSI-P / M	50	24 (48)	50 (100)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20% vs. Supine-Pre-PP
Rossi S (2022) [62]	Italy	NRSI-P / SC	25	25 (100)	25 (100)	NA	Immediate-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP
Camporota L (2022) [63]	Italy; UK; France	NRSI-R / M	376	376 (100)	220 (58.5)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP
Petit M (2022) [64]	France	NRSI-R / SC	298	64 (21)	0 (0)	298 (100)	End-PP	**Respiratory mechanics**: Crs increase ≥ 3 mL/cmH_2O vs. Supine-Pre-PP
Cunha MCA (2022) [65]	Brazil	NRSI-R / M	574	574 (100)	574 (100)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP
Kawakami A (2022) [66]	Japan	NRSI-R / SC	54	54 (100)	54 (100)	0 (0)	End-PP / Post-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 1 mmHg vs. Supine-Pre-PP **Oxygenation**: PaO_2/FiO_2 increase ≥ 1 mmHg Post-PP vs. Supine-Pre-PP
Sanabria-Rodríguez OO (2023) [67]	Colombia	NRSI-R / SC	724	724 (100)	724 (100)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20% vs. Supine-Pre-PP
Rebelo Oliveira SM (2023) [68]	Portugal	NRSI-R / SC	52	52 (100)	52 (100)	3 (5.8)	Post-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 1 mmHg Post-PP vs. Supine-Pre-PP
Heldeweg MLA (2023) [69]	Netherlands	NRSI-P / SC	79	79 (100)	79 (100)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP
Cunha MCA (2023) [70]	Brazil	NRSI-R / M	223	223 (100)	223 (100)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP
Morais CCA (2023) [71]	USA; Brazil	NRSI-P / M	22	22 (100)	22 (100)	NA	Early-PP	**Respiratory mechanics**: Crs increase > 10% vs. Supine-Pre-PP
Lai C (2024) [72]	France	NRSI-P / SC	50	50 (100)	50 (100)	0 (0)	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP
Jørgensen VL (2024) [73]	Denmark	NRSI-R / M	68	44 (65)	68 (100)	68 (100)	End-PP	**Oxygenation**: FiO_2+FsO_2 decrease > 20% vs. Supine-Pre-PP **Respiratory mechanics**: Crs increase ≥ 3 mL/cmH_2O vs. Supine-Pre-PP
Zadek F (2024) [74]	Italy	NRSI-R / SC	125	125 (100)	125 (100)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP **CO_2clearance**: ΔVR decrease > 0 vs. Supine-Pre-PP
Huai J (2024) [75]	China	NRSI-R / SC	27	27 (100)	NA	27 (100)	Early-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg vs. Supine-Pre-PP
Liang H (2024) [76]	China	NRSI-R / SC	104	104 (100)	23 (22)	0 (0)	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 99.465% vs. Supine-Pre-PP **CO_2clearance**: $PaCO_2$ increase ≤ 3.15% vs. Supine–Pre-PP
Gonzalez C (2024) [77]	Argentina	NRSI-P and R / SC	273	273 (100)	273 (100)	NA	End-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 50% vs. Supine-Pre-PP
Yang Y (2025) [78]	China	NRSI-P / M	29	29 (100)	15 (52)	NA	Early-PP	**Oxygenation**: SpO_2/FiO_2 increase ≥ 20% vs. Supine-Pre-PP **Other**: EIT V/Q Matching improve vs. Supine-Pre-PP
Yan Y (2025) [79]	China	NRSI-R / SC	175	175 (100)	NA	11 (6.3)	Post-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20 mmHg Post-PP vs. Supine-Pre-PP
Wang R (2025) [80]	China	NRSI-P / M	77	77 (100)	15 (19.5)	0 (0)	Early-PP	**Other**: EIT V/Q Matching improve ≥ 10% vs. Supine-Pre-PP

Table 1 (continued)

Author (year)	Country	Study design	Total patients *n*	Patients proned *n* (%)	COVID19 patients *n* (%)	ECMO PP *n* (%)	Timing of response assessment	Responder definition
Chang K-W (2025) [81]	Taiwan	NRSI-R / M	138	138 (100)	2 (1.4)	0 (0)	Post-PP	**Oxygenation**: PaO_2/FiO_2 increase ≥ 20% or ≥ 20 mmHg Post-PP vs. Supine-Pre-PP **CO_2clearance**: $PaCO_2$ decreased ≥ 1 mmHg Post-PP vs. Supine-Pre-PP
De Rosa S (2025) [42]	International (53)	NRSI-P and R / M	1816	1816 (100)	1816 (100)	29 (1.6)	End-PP / Post-PP	**Oxygenation**: PaO_2/FiO_2 increase > 0 mmHg vs. Supine-Pre-PP **Oxygenation**: PaO_2/FiO_2 increase > 0 mmHg Post-PP vs. Supine-Pre-PP
Wu Y (2025) [38]	China	NRSI-R / SC	1078	1078 (100)	85 (7.9)	0 (0)	End-PP	**Oxygenation**: PaO_2/FiO_2 increase > 20 mmHg vs. Supine-Pre-PP **Respiratory mechanics**: a posteriori definition based on median ΔMP

*Three patients were treated with extracorporeal CO_2 removal combined with low-frequency positive-pressure ventilation

§ Four of the 32 enrolled patients were excluded from the analysis because they had chronic respiratory insufficiency rather than ARDS

[+] Analysis of response performed on subset of 78 patients

The categorization of "Timing of Response Assessment" was introduced by the authors of this review for harmonization purposes and does not necessarily reflect the terminology used in the original studies. Specifically, response was classified as Immediate (< 1 h after initiation of prone positioning), Early (< 4 h), End-PP (assessed immediately before return to the supine position), Post-PP (assessed after resupination), or Other when alternative timing criteria were applied. When multiple time points were reported, the principal or latest evaluable assessment was included in the table

ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; ECMO-PP = patients receiving prone positioning while already on ECMO support at the time of response assessment; EIT = electrical impedance tomography; FiO_2 = fraction of inspired oxygen; FsO_2 = fraction of oxygen in the ECMO sweep gas; NRSI = non-randomized study of interventions; R: retrospective; P: prospective; PP = prone positioning; RCT = randomized controlled trial; SC = single-center; M = multicenter; PaO_2 = arterial partial pressure of oxygen; $PaCO_2$ = arterial partial pressure of carbon dioxide; SpO_2 = peripheral oxygen saturation; V/Q = ventilation/perfusion; ΔEELV = change in end-expiratory lung volume; Crs = respiratory system compliance; ΔVR = change in ventilatory ratio; ODCL = overdistension–collapse loss; Vtdep/Vtndep = tidal volume distributed to dependent vs. non-dependent lung regions

1,994 records underwent title and abstract screening, of which 1,834 were excluded. A total of 170 full-text articles were assessed for eligibility, and 66 studies [16–81] met the inclusion criteria and were included in the review, for a total of 10,188 patients, of whom 9120 (93%) underwent prone positioning and were evaluable for responsiveness.

The PRISMA 2020 flow diagram summarizing the selection process is reported in Additional File 2.

Reasons for exclusion of the 104 full-text articles not meeting the inclusion criteria are detailed in Additional File 3 and mainly included wrong outcome, wrong publication type, not English language, wrong study design, wrong population, or duplicate publications.

Study characteristics

The main characteristics of the 66 included studies [16–81] are summarized in Table 1.

Of the 66 included studies, 46 (70%) were single-centre [17–25, 28–30, 32–38, 40, 41, 43–48, 50, 53, 55, 57–60, 62, 64, 66–69, 72, 74–77, 79] and 20 (30%) were multicentre studies [16, 26, 27, 31, 39, 42, 49, 51, 52, 54, 56, 61, 63, 65, 70, 71, 73, 78, 80, 81]. Sixty-five studies (98%) were non-randomized observational [16–27, 29–81], including 39 prospective [16, 18–26, 30–37, 39–41, 43–47, 49, 50, 54–56, 59, 61, 62, 69, 71, 72, 78, 80], 24 retrospective [17, 27, 29, 38, 48, 51–53, 57, 58, 60, 63–68, 70, 73–76, 79, 81], and 2 mixed prospective–retrospective cohorts [42, 77], while only one study was a randomized controlled trial [28].

Studies were conducted between the late 1980s and the 2020s across Europe, North and South America, and Asia. Sample size varied widely, ranging from small physiological series (≤ 20 patients; 19 studies) to large cohorts including more than 300 patients (8 studies).

All studies included adult patients with acute respiratory failure fulfilling criteria for acute lung injury or ARDS according to contemporaneous definitions [12, 82]. A subset of cohorts focused on COVID-19–related ARDS [38, 42, 50–56, 58, 59, 61–63, 65–74, 76–78, 80, 81], and several studies reported data on patients supported with veno-venous extracorporeal membrane oxygenation (VV ECMO) [17, 37, 42, 46, 47, 50, 53, 56, 64, 68, 73, 75, 79]. The proportion of COVID-19 and ECMO patients across studies is reported in Table 1.

Risk of bias

The results of the risk-of-bias assessment is reported in Additional Files 4 and 5. For the outcome proportion of responders, 34 studies were judged at low risk [16, 18, 19, 21, 22, 29–31, 34, 36, 38, 39, 42, 47, 51–56, 58, 59, 63–67, 69, 70, 72, 74, 77, 79, 81] and 32 at moderate risk of bias [17, 20, 23–28, 32, 33, 35, 37, 40, 41, 43–46, 48–50, 57, 60–62, 68, 71, 73, 75, 76, 78, 80]. All studies raised concerns regarding external validity, due to single-centre design and non-representative cohorts. For the outcome of mortality, all except six studies [16, 31, 42, 63, 76, 80] were judged at critical risk of bias, due to concerns regarding the domain "Bias due to Confounding". One study was judged at critical risk of bias due to "Bias due to selection of participants" [76]. The remaining five studies [16, 31, 42, 63, 80], judged at overall serious risk of bias, raised serious concerns regarding the domain "Bias due to Confounding" and "Bias in selection of the reported results".

Responsiveness to prone positioning

Definitions of responsiveness showed substantial heterogeneity across studies. As summarized in Tables 1 and 2, most investigations relied on changes in oxygenation to classify responders, whereas far fewer assessed carbon dioxide clearance, respiratory mechanics, or V/Q matching.

Specifically, 62 studies (94%) defined responsiveness based on oxygenation criteria [16–48, 50–63, 65–70, 72–79, 81], 14 studies (21%) [16, 27, 29, 31, 36, 39, 48, 51, 52, 57, 58, 74, 76, 81] included at least one criterion related to carbon dioxide clearance, 5 studies (8%) [38, 49, 64, 71, 73] used respiratory mechanics to define responsiveness, although only 4 [49, 64, 71, 73] reported responder proportions and were included in the quantitative analysis, and 2 studies (3%) [78, 80] used V/Q matching, primarily assessed by electrical impedance tomography.

These definitions were assessed using arterial blood gas (ABG) analysis or SpO_2 for oxygenation criteria in 94% (62/66) of studies. Similarly, dead space evaluation was performed in 21% (14/66) of studies, most often indirectly, either as changes in CO_2 or through calculation of the ventilatory ratio (VR). Changes in respiratory mechanics were defined as variations in compliance in 6% (4/66) of studies, while alternative techniques, such as electrical impedance tomography (EIT), were only rarely employed.

Regarding the timing of response assessment, 22 studies (33%) [20, 23–26, 33, 35, 37, 40, 41, 43–45, 47, 49, 57, 60, 62, 71, 75, 78, 80] evaluated response during the early phase of the prone session, either within the first hour (Immediate-PP) or within the first 4 h (Early-PP). Thirty-seven studies (56%) [16, 18, 21, 22, 27–31, 34, 36, 38, 39, 42, 46–48, 50–53, 55, 58, 59, 61, 63–67, 69, 70, 72–74, 76, 77] assessed response at the end of the prone session, immediately before returning the patient to the supine position (End-PP), while 18 studies (27%) [17, 19, 20, 24, 32, 33, 39, 42, 45, 52, 54, 56, 57, 59, 66, 68, 79, 81] evaluated response after return to the supine position (Post-PP). Two studies (3%) [32, 54] assessed response at 7 days after resupination. Eleven studies evaluated response at

Table 2 Definitions of responsiveness to PP across all included studies, stratified by physiological domain

A. Oxygenation-based definitions			B. CO_2 clearance / dead-space definitions		
	PP	**Post-PP**		**PP**	**Post-PP**
Ø PaO_2/FiO_2 increase ≥ 20 mmHg	21	5	Ø $PaCO_2$ decreased ≥ 1 mmHg	3	1
Ø PaO_2/FiO_2 increase ≥ 20%	16	4	Ø ΔVR decrease > 0	2	0
Ø PaO_2 increase ≥ 10 mmHg	3	0	Ø $PaCO_2$ equal or decreased	1	1
Ø PaO_2/FiO_2 increase ≥ 15%	3	1	Ø $PaCO_2$ decreased > 0.9 mmHg	1	0
Ø PaO_2/FiO_2 increase ≥ 50%	2	1	Ø $PaCO_2$ decreased ≥ 2 mmHg	1	0
Ø PaO_2/FiO_2 increase ≥ 30%	2	1	Ø Increase in VE: PaCO2 ≥ 41.7%	1	0
Ø PaO_2 increase ≥ 20 mmHg	2	0	Ø ΔVR decrease ≥ 0	1	0
Ø PaO_2/FiO_2 increase ≥ 10%	2	0	Ø $PaCO_2$ increase ≤ 3.15%	1	0
Ø PaO_2/FiO_2 increase ≥ 100%	1	0	Ø $PaCO_2$ decreased ≥ 2%	0	1
Ø PaO_2/FiO_2 increase ≥ 40%	1	0	**C. Respiratory mechanics definitions**		
Ø PaO_2/FiO_2 increase ≥ 40 mmHg	1	0		**PP**	**Post-PP**
Ø FiO_2+FsO_2 decrease > 20%	1	0	Ø Crs increase ≥ 3 mL/cmH_2O	2	0
Ø SpO_2/FiO_2 increase ≥ 20%	1	0	Ø EIT-derived improvement in lung protection	1	0
Ø PaO_2 increase ≥ 7 mmHg	1	0	Ø Crs increase > 10%	1	0
Ø PaO_2/FiO_2 increase ≥ 1 mmHg	1	2	**D. Other physiological domains**		
Ø PaO_2/FiO_2 increase > 0 mmHg	1	1		**PP**	**Post-PP**
Ø PaO_2/FiO_2 ≥300 mmHg	0	1	Ø EIT V/Q Matching improve	1	0
Ø PaO_2/FiO_2 increase ≥ 60%	0	1	Ø EIT V/Q Matching improve ≥ 10%	1	0

Table 2 summarizes all definitions of responsiveness used in the included studies, grouped by physiological domain: Panel A: oxygenation, Panel B: CO_2 clearance/dead space, Panel C: respiratory mechanics, and Panel D: other advanced method (e.g., V/Q matching). "Prone positioning (PP)" refers to studies assessing the physiological response during the prone session, while "Post-PP" refers to assessments performed after returning the patient to the supine position

PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; SpO_2, peripheral oxygen saturation; FsO_2, ECMO supplemental oxygen fraction; ΔVR, change in ventilatory ratio; VE, minute ventilation; Crs, respiratory system compliance; EIT, electrical impedance tomography; V/Q, ventilation–perfusio

more than one time point [20, 24, 33, 39, 42, 45, 47, 52, 57, 59, 66].

Overall, the prone positioning protocols adopted were heterogeneous across the included studies. The duration of the index prone session ranged from less than 1 h in early physiological studies to extended sessions up to 16–18 h in more contemporary cohorts.

Pooled proportions of oxygenation response

Oxygenation response, defined as a change of PaO_2/FiO_2 from supine to PP, was adopted as definition by 53 studies [16, 18, 20–31, 33–48, 50–53, 55, 58–63, 65–67, 69, 70, 72–78].

Among studies adopting oxygenation-based definitions, 37 (70%) used absolute or relative PaO_2/FiO_2 increases of approximately 20 mmHg or 20%, while 16 studies (30%) applied alternative thresholds, including smaller absolute PaO_2 increases (7–10 mmHg), higher proportional changes (≥ 40–60%), or delayed criteria such as achieving PaO_2/FiO_2 ≥300 mmHg (Table 1).

The pooled proportion of responders was estimated as 68% (95% C.I. 63–72%; Fig. 1). However, heterogeneity was considerable with an $I^2 = 91.4\%$.

Oxygenation response, defined as a change of PaO_2/FiO_2 from supine to re-supine position after PP (Post-PP), was adopted as definition by 17 studies [17, 19, 20, 24, 32, 33, 39, 42, 45, 54, 56, 57, 59, 66, 68, 79, 81]. The analysis considering these studies showed a pooled proportion of responders of 59% (95% C.I. 51–67%; see Additional File 6). Heterogeneity remained considerable with an $I^2 = 92.2\%$.

Other definitions

Twenty-one of the 66 included studies (32%) evaluated responsiveness using physiological variables other than, or in addition to, oxygenation (Table 1). These studies defined response based on carbon dioxide clearance, respiratory mechanics, or V/Q matching.

Carbon dioxide–based definitions included reductions in $PaCO_2$ (typically ≥ 1–2 mmHg or relative percentage decreases), improvements in dead-space surrogates such as changes in ventilatory ratio (ΔVR), or combined oxygenation–$PaCO_2$ criteria [16, 27, 29, 31, 36, 39, 48, 51, 52, 57, 58, 74, 76, 81].

Five studies [38, 49, 64, 71, 73] used respiratory mechanics to classify responders; response criteria included increases in respiratory system compliance (≥ 3 mL/cmH_2O or > 10%) or electrical impedance tomography (EIT)–derived markers indicating improved lung homogeneity and increased end-expiratory lung volume. Only four [49, 64, 71, 73] of these studies reported responder proportions and were therefore included in the quantitative analysis.

Two studies [78, 80] assessed response using V/Q matching, primarily based on EIT-derived V/Q indices.

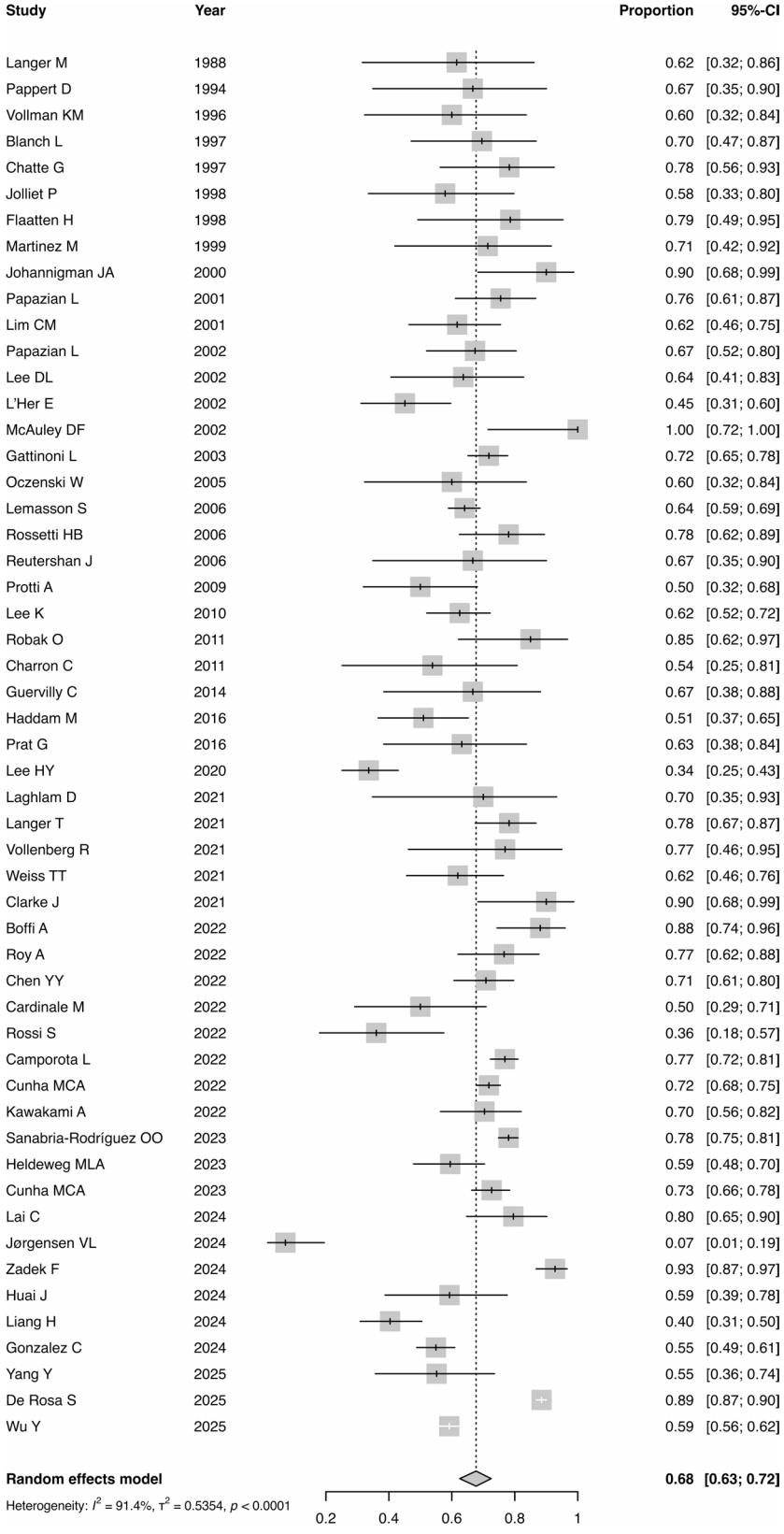

Fig. 1 Forest plot reporting pooled proportions of oxygenation response defined as a change of PaO_2/FiO_2 from supine to prone position

The pooled proportion of response defined by methods different than oxygenation ranged from 45% to 53% (Overall estimate 47%, 95% C.I. 42–52%), with a substantial to considerable heterogeneity and a non-significant subgroup effect ($P = 0.84$), see Fig. 2.

Results of further analyses conducted on sub-populations of patients (i.e. COVID-19, ECMO and ARDS defined as per Berlin definition) are available at Additional Files 7, 8 and 9.

Responsiveness and risk of mortality

Overall, 32 included studies reported raw data on mortality in responders and non-responders [16, 18, 19, 29, 31, 34, 38, 39, 42, 48, 54, 56, 57, 59–61, 63–68, 70–72, 74–77, 79–81]. Of those, 6 had identified a post-hoc definition of responder based on mortality and were thus excluded from the quantitative analysis on mortality [39, 48, 56, 57, 66, 76].

Eleven studies out of twenty-six reported a significantly reduced unadjusted risk of mortality in the responder cohort. We decided not to proceed to a meta-analysis, due to the critical risk of bias of the included non-randomized studies [13] the unadjusted nature of reported estimates and the considerable heterogeneity (see Additional File 10). The sensitivity analysis conducted pooling data from the five studies at serious risk of bias only (see Additional File 11) showed a significantly reduced risk of mortality in the responder cohort (OR 0.41 [95% C.I. 0.25–0.68], $I^2 = 78\%$.

No publication bias was noted (see Additional File 12, Egger $p = 0.172$).

We conducted a sensitivity analysis pooling data from the three studies reporting adjusted estimates and considering the effects of confounders. The point estimate suggests a reduced risk of adjusted mortality in the responder cohort, but the confidence interval crossed unity (OR 0.74, 95% C.I. 0.54–1.03, see Additional File 13).

Discussion

The main findings of our study are: (a) the most frequent definition of response to PP is based on oxygenation change from supine to PP; (b) the pooled proportion of responders varies across studies, ranging from 45 to 68%; (c) the overall heterogeneity across the studies is considerable, and remains from substantial to considerable even after subgroup or restricted analyses, mainly due to clinical heterogeneity in prone positioning protocols (e.g. duration, number of cycles) and responsiveness assessment (e.g. adopted cutoff for each definition, timing of response assessment), reflecting the complex and multifaceted interpretation of the physiological effects of this intervention.

Current evidence [1], strengthened by the findings of major randomized trials [1, 83–85] and by the clinical experience from the COVID-19 pandemic [51] supports the beneficial role of prone positioning in patients with moderate to severe ARDS. However, clinicians still need clear indications on how to identify the patients most likely to benefit from the intervention.

Most studies classified responders according to improvement in oxygenation, typically a ≥ 20 mmHg or ≥ 20% increase in PaO_2/FiO_2, whereas fewer evaluated CO_2 clearance, respiratory mechanics, or V/Q matching. This heterogeneity mirrors the complexity of ARDS itself: reducing a multidimensional physiological response to a single parameter, such as PaO_2/FiO_2, may be overly simplistic or even misleading. Moreover, patients may show discordant responses to prone positioning, with no improvement in oxygenation despite enhanced CO_2 clearance, or vice versa. As proposed by Gattinoni et al. [31], improvements in PaO_2 without $PaCO_2$ reduction likely result from perfusion redistribution, whereas in $PaCO_2$ responders alveolar recruitment predominates. In the former, chest wall impairment outweighs recruitment; in the latter, recruitment overcomes chest wall restriction. This also explains the difficulty in interpreting respiratory mechanics: prone positioning increases chest wall stiffness, and total respiratory system compliance may decrease despite improved lung compliance. These considerations underscore the limitations of binary definitions of responsiveness and support the need for individualized physiological assessment.

Heterogeneity across the existing literature still limits the opportunity to provide certain answers to the main clinical questions on response assessment, i.e. best timing of assessment, the use of single vs. composite parameters, and threshold selection in relation to outcomes. Regarding timing, early oxygenation changes primarily reflect the acute redistribution of perfusion toward previously atelectatic dorsal lung units and may not capture the sustained morphological effects of prolonged proning, including alveolar stabilization, secretion drainage, and resolution of compression atelectasis. Post-prone assessment after returning to supine position is physiologically grounded, as a maintained oxygenation improvement in the gravitationally unfavorable supine position may indicate durable structural lung remodeling rather than a mere perfusion redistribution.

Notably, responses to prone positioning may vary over time. Improvements in oxygenation or respiratory mechanics may be absent in some patients or may occur early in the disease but then vanish after initial cycles of prone positioning. Time-dependent factors, such as delays to invasive support, timing of the first prone session after intubation, and progression of lung injury, may influence the physiological response.

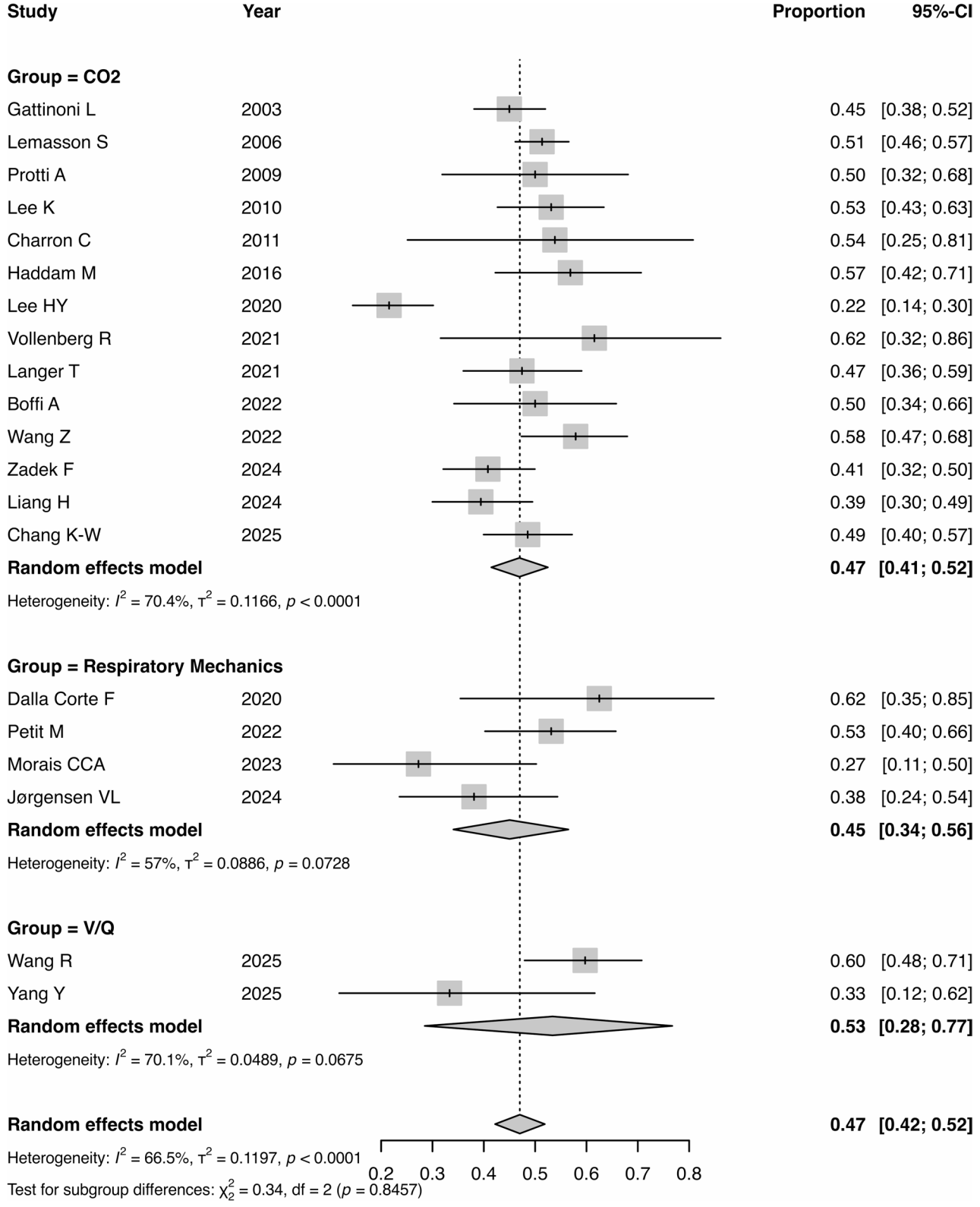

Fig. 2 Forest plot reporting pooled proportions of response to prone position, grouped by definition different from oxygenation

Regarding parameter selection, PaO_2/FiO_2 is a global and indirect index of V/Q matching, heavily influenced by FiO_2 settings, cardiac output, and intrapulmonary shunt, without distinguishing recruitment from redistribution. CO_2-derived parameters reflect redistribution of ventilation toward better-perfused units and carry independent prognostic value. Respiratory system compliance captures improvements in the global stress-strain relationship more directly linked to VILI reduction than oxygenation alone. Composite definitions incorporating these domains may offer a more complete physiological assessment of the prone response, though currently underutilized. Such physiological considerations and results of our analysis may offer a comprehensive background to inform the design of future consensus definitions and research.

In patients receiving extracorporeal respiratory support the definition of response based on oxygenation changes is inherently imprecise, because ECMO directly alters gas exchange [86, 87]. Our data show that the rate of "response" in ECMO patients ranges from 46 to 83%, depending on the definition; however, this estimate should be interpreted with caution, also in light of the most recent evidence on this topic [88]. This highlights the need for alternative metrics and for physiologically grounded definitions tailored to this subgroup.

Finally, despite both unadjusted and adjusted analyses yielded point estimates suggesting a lower mortality risk among responders, the relationship between surrogate physiological markers of response to prone positioning and mortality or other clinical outcomes remains uncertain. Risk of bias, residual confounding, between-study heterogeneity, and imprecision precluded robust conclusions regarding the association between physiological responsiveness and survival. Although prone positioning remains a safe and widely applicable intervention and will likely continue to be used broadly [89], systematic post-proning assessment may help inform the appropriateness of repeated sessions or the consideration of alternative strategies. Ultimately, identifying patients most likely to benefit and individualizing proning strategies may improve clinical outcomes.

Taken together, our evidence synthesis suggests that a structured consensus process on how to define response to PP, in order to homogenize future research designs and help shaping decisions in clinical practice is needed.

Studying patient phenotypes may also help identify, even before proning, which individuals are more likely to benefit from the intervention.

Limitations

The main limitations of this systematic review and meta-analysis stem from the characteristics of the available evidence. First, substantial heterogeneity was observed across studies reporting the proportion of patients classified as responders to prone positioning; to mitigate this, we conducted clinically relevant subgroup and sensitivity analyses. However, a certain degree of heterogeneity remained. Indeed, the included studies span more than four decades (late 1980s to 2025), encompassing major revisions of the ARDS definition and profound changes in standard-of-care management (lung-protective ventilation, prolonged prone positioning, neuromuscular blockade, and extracorporeal membrane oxygenation), which likely influenced heterogeneity. Second, the interval between intubation and the first prone session varied widely among studies. Third, most studies evaluated only the response to the initial prone session, whereas subsequent sessions, often multiple in clinical practice, were rarely considered. Thus, our analysis focused on response to the index proning session and no conclusions could be drawn on responsiveness maintenance over repeated cycles [90]. Fourth, responsiveness was generally assessed without accounting for concomitant changes in mechanical ventilation settings (e.g., tidal volume, PEEP, or driving pressure) or hemodynamic variations. Fifth, pulmonary and extrapulmonary ARDS differ in their recruitability patterns and morphological response to prone positioning but the majority of included studies did not systematically stratify their cohorts by pulmonary vs. extrapulmonary origin of ARDS and the included cohorts were mostly mixed, thus hampering any analysis to address this source of heterogeneity. Sixth, meta-regression to formally investigate the contribution of timing of response assessment and threshold category to between-study heterogeneity was not performed, due to non-independence of definitions within studies. Many studies provided data for more than one timing of assessment, precluding the treatment of these data points as independent observations. Finally, few studies reported adjusted mortality data, limiting the ability to explore associations with this outcome while adequately controlling for confounding.

Conclusions

More than two third of patients with ARDS undergoing PP are classified as responders. However, the definition of responsiveness to prone positioning is highly heterogeneous across literature, reflecting the complex physiology underlying this intervention. Most studies rely on oxygenation, and fewer consider CO_2 clearance, respiratory mechanics or other methods to assess responsiveness. A more comprehensive, multidimensional approach may be needed to better characterize the response and guide clinical practice. This review provides a basis for future research to reach a consensus on validated definitions.

Abbreviations

ARDS	Acute Respiratory Distress Syndrome
PP	Prone Position
ICU	Intensive Care Unit
PaO_2	Arterial partial pressure of oxygen
$PaCO_2$	Arterial partial pressure of carbon dioxide
FiO_2	Fraction of inspired oxygen
PEEP	Positive end–expiratory pressure
Crs	Respiratory system compliance
V/Q	Ventilation–perfusion
VILI	Ventilator–induced lung injury
ECMO	Extracorporeal Membrane Oxygenation
VV	ECMO–Veno–venous extracorporeal membrane oxygenation
EIT	Electrical Impedance Tomography
ΔVR	Change in ventilatory ratio
MP	Mechanical Power
EELV	End–expiratory lung volume
CT	Computed Tomography
C.I.	Confidence interval
OR	Odds ratio
I^2	I–squared statistic
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta–Analyses
ROBINS	I–Risk Of Bias In Non–randomized Studies of Interventions
RCT	Randomized Controlled Trial
GLMM	Generalized Linear Mixed Model
SD	Standard Deviation
IQR	Interquartile Range

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-026-06081-y.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

Supplementary Material 6.

Supplementary Material 7.

Supplementary Material 8.

Supplementary Material 9.

Supplementary Material 10.

Supplementary Material 11.

Supplementary Material 12.

Supplementary Material 13.

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Author contributions

Caccioppola Alessio: Conceptualization, Investigation, Formal analysis, Validation, Writing original draft. Ippolito Mariachiara: Investigation, Methodology, Formal analysis, Validation, Writing original draft. Cortegiani Andrea: Methodology, Validation, Formal analysis, Supervision, Writing review & editing. Guérin Claude: Conceptualization, Investigation, Validation, Supervision, Writing review & editing. Grasselli Giacomo: Conceptualization, Methodology, Supervision, Writing review & editing.

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Data availability

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

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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