

Table S1. Search strategy for each database

Ovid Medline (via Ovid SP)	exp Prostaglandins/ or prostaglandin*.ti,ab. or pgi2.mp. or pgx.mp. or "prostaglandin i 2".mp. or "prostaglandin l2".mp. or "prostaglandin x".mp. or "u 53217".mp. or prostacyclin.mp. or exp Epoprostenol/ or epoprostenol.ti,ab. Or (35121-78-9 or 4k04iq1of4 or dcr9z582x0 or epoprostanol or epoprostenol or epoprostenol sodium or flolan or veletri).mp or (Treprostinil or tyvaso or remodulin).mp. or Iloprost/ or iloprost.ti,ab. Or (78919-13-8 or iloprost or ciloprost or jed5k35ygl or ventavis or zk 36374 or zk-36374 or zk36374).mp. or exp Alprostadil/ or alprostadil.ti,ab. Or (745-65-3 or alprostadil or caverject or edex or f5td010360 or lipo pge1 or lipo-pge1 or minprog or muse or pge1 or pge1alpha or prostaglandin e1 or prostaglandin e1alpha or prostavasin or prostin vr or prostine vr or sugiran or vasaprostan or viridal).mp. or (15au81 or bw 15auor bw15au or hexadecyl treprostinil or ins 1009 or ins1009 or lrx 15 or lrx15 or orenitram or remodulin or trepulumix or tyvaso or u 62840 or u62840 or uniprost or ut 15 or ut 15c or ut15 or ut15c or iloprost).mp. or exp iloprost/ or (ciloprost or endoprost or ilomedin or ilomedine or sh 401 or sh401 or shl 401 a or shl 401a or shl401a or ventavisor zk 36374 or zk 36375or zk36374 or zk36375).mp. or alprostadil.mp. or exp prostaglandin E1/ or (745-65-3 or alista or aloprastadil or alprestil or alprostadil or alprostanor alprostapintor alprostin or alprox or alyprostor befar or bondil or caverject or caverjet or edex or eglandin or femprox or karon or lyple or minprog or muse or pg e1 or pge 1 or pge1 or pridax or prink or promostan or prostaglandin e 1 or prostaglandine e1 or prostin or prostine vr or prostivas or topiglan or vasostenoon or virirec or vitaros or vytaros or prostavasin or sugiran or vasaprostan or viridal).mp. AND exp Respiratory Distress Syndrome/ or (ards or ((adult or acute or idiopathic) adj2 respiratory distress) or "respiratory distress syndrome" or "shock lung").mp. or "stiff lung".mp. or exp acute lung injury/ or exp ventilator-induced lung injury/ 42 not or ALI.mp. or respiratory failure.mp. or exp Respiratory Insufficiency or exp Pneumonia/ or pneumonia.mp. or pulmonary edema.mp. or exp Pulmonary Edema/ AND exp Outcome Assessment, Health Care/ OR exp Mortality/ or mortality.sh. or exp Survival/ or exp Survival Analysis/ exp "Quality of Life"/ OR exp Pain Measurement/ or Pain/ or Health/ or exp Health Status Indicators/ or exp Health Status/ or (respond* or response* or failure* or mortality or fatal* or death or dead or deaths).mp. or respond* or response* or failure* or mortality or fatal* or death or dead or deaths).mp. or (regress* or surviv* or nonsurviv* or cure or cures or "quality of life").mp. or ("qol" or HRQL or "life quality").ti,ab. Or (morbidit* or adverse or "side effect* side effects" or event or events or nausea or nauseous or vomit* or emesis or comfort* or pain or painful or painfree or stress or analges*).mp. or Oxygen/bl [Blood] or oxygenation.mp.
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	<p>NOT exp Animals/ not (exp Animals/ and exp Humans/) NOT case report*.mp.</p>
<p>Embase (via Ovid SP)</p>	<p>exp prostaglandin/ or (prostaglandin* or pgi2 or pgx or "prostaglandin i 2" or "prostaglandin l2" or "prostaglandin x" or "u 53217").mp. or exp prostacyclin/ or prostacyclin.mp. or Epoprostenol.mp. or (35121-78-9 or prostaglandin* or pgi2 or pgx or "prostaglandin i 2" or "prostaglandin l2" or "prostaglandin x" or "u 53217").mp. or treprostinil.mp. or exp treprostinil/ or (15au81 or bw 15au bw15au or hexadecyl treprostinil or ins 1009 or ins1009 or lrx 15 or lrx15 or orenitram or remodulin or trepulumix or tyvaso or u 62840 or u62840 or uniprost or ut 15 or ut 15c or ut15 or ut15c).mp. or iloprost.mp. or exp iloprost/ or (ciloprost or endoprost or ilomedin or ilomedine or sh 401 or sh401 or shl 401 a or shl 401a or shl401a or ventavisor zk 36374 or zk 36375 or zk36374 or zk36375).mp. or alprostadil.mp. or exp prostaglandin E1/ or (745-65-3 or alista or aloprastadil or alprestil or alprostadil or alprostanor alprostapintor alprostin or alprox or alyprostor befar or bondil or caverject or caverjet or edex or eglandin or femprox or karon or lypile or minprog or muse or pg e1 or pge 1 or pge1 or pridax or prink or promostan or prostaglandin e 1 or prostaglandine e1 or prostin or prostine vr or prostivas or topiglan or vasostenoon or virirec or vitaros or vytaros or prostavasin or sugiran or vasaprostan or viridal).mp. AND respiratory distress syndrome/ or exp acute lung injury/ or exp adult respiratory distress syndrome/ or exp idiopathic respiratory distress syndrome/ or (ards or ((adult or acute or idiopathic) adj2 respiratory distress) or "respiratory distress syndrome" or "shock lung").mp. or "stiff lung".mp. or exp ventilator induced lung injury/ or VILI.mp. or "ventilator induced lung injury".mp. or ALL.mp. or exp respiratory failure/ or exp acute respiratory failure/ or exp chronic respiratory failure/ or exp lung insufficiency/ or pneumonia.mp. or exp pneumonia/ or pulmonary edema.mp. or exp lung edema/ AND exp outcome assessment/ or (outcome adj2 (measure* or assess*)).mp. or exp mortality/ or exp survival analysis/ or exp survival/ or exp pain measurement/ or exp pain/ or exp health status/ or health/ or exp health status indicator/ or (response* or respond* or failure* or mortality or fatal* or death or dead or deaths).mp. or ("passed away" or demise* or recurren* or progression or progressed or relaps* or growth or grew or growing).mp. or (regress* or surviv* or nonsurviv* or cure or cures or "quality of life").mp. or ("qol" or HRQL or "life quality").ti,ab. Or (morbidit* or adverse or "side effect" or "side effects" or event or events or nausea or nauseous or vomit* or emesis or comfort or pain or painful or painfree or stress or analges*).mp. or (oxygen adj2 blood).mp. or exp blood oxygenation/ NOT exp Animal/ not (exp animal/ and exp Humans/) NOT exp case report/ or case report*.mp.</p>

<p>CINAHL (via EBSCOhost)</p>	<p>(MH "Prostaglandins+") OR "prostacyclin" OR (MH "Epoprostenol") OR prostaglandin* or pgi2 or pgx or "prostaglandin i 2" or "prostaglandin l2" or "prostaglandin x" or "u 53217 or "treprostinil" or 15au81 or bw 15auor bw15au or hexadecyl treprostinil or ins 1009 or ins1009 or lrx 15 or lrx15 or orenitram or remodulin or trepulumix or tyvaso or u 62840 or u62840 or uniprost or ut 15 or ut 15c or ut15 or ut15c or (MH "Iloprost") OR "iloprost" or ciloprost or endoprost or ilomedin or ilomedine or sh 401 or sh401 or shl 401 a or shl 401a or shl401a or ventavisor zk 36374 or zk 36375or zk36374 or zk36375 or alista or aloprastadil or alprestil or alprostadil or alprostanor alprostapintor alprostin or alprox or alyprostor befar or bondil or caverject or caverjet or edex or eglandin or femprox or karon or lyle or minprog or muse or pg e1 or pge 1 or pge1 or pridax or prink or promostan or prostaglandin e 1 or prostaglandine e1 or prostin or prostine vr or prostivas or topiglan or vasostenoon or virirec or vitaros or vytaros or prostavasin or sugiran or vasaprostan or viridal</p> <p>AND</p> <p>(MH "Respiratory Distress Syndrome") OR (MH "Acute Lung Injury") OR (MH "Ventilator-Induced Lung Injury") OR (MH "Respiratory Distress Syndrome, Acute") OR ards or ((adult or acute or idiopathic) N2 respiratory distress OR "shock lung" or "stiff lung" Or vili OR ALI Or "lung dysplasia" OR (MH "Respiratory Failure") Or "chronic respiratory failure" OR "lung insufficiency" OR (MH "Pulmonary Edema") OR (MH "Pneumonia+") Or (pulmonary or lung) N2 edema</p> <p>AND</p> <p>(MH "Outcomes (Health Care)") OR (MH "Outcome Assessment") Or outcome N2 (measure* or assess*) OR</p> <p>(MH "Cause of Death") Or mortality Or (MH "Survival Analysis+") OR (MH "Survival") Or (MH "Pain Measurement") Or (MH "Pain+") OR (MH "Health") OR (MH "Health Status") OR (MH "Health Status Indicators") Or response* or respond* or failure* or mortality or fatal* or death or dead or deaths OR "passed away" or demise* or recurren* or progression or progressed or relaps* or growth or grew or growing Or regress* or surviv* or nonsurviv* or cure or cures or "quality of life" Or TI (("qol" or HRQL or "life quality")) OR AB (("qol" or HRQL or "life quality")) OR (MH "Oxygen/BL") OR blood oxygenation morbidity* or adverse or "side effect" or "side effects" or event or events or nausea or nauseous or vomit* or emesis or comfort or pain or painful or painfree or stress or analges*</p> <p>NOT</p> <p>case report*</p>
<p>Cochrane Reviews and Central (via Wiley)</p>	<p>(prostaglandin* or pgi2 or pgx or "prostaglandin i 2" or "prostaglandin l2" or "prostaglandin x" or "u 53217"):ti,ab,kw Or</p> <p>MeSH descriptor: [Prostaglandins] explode all trees or prostacyclin* or Epoprostenol or 4k04iq1of4 or dcr9z582x0 or epoprostanol or epoprostenol sodium or flolan or veletri or Treprostinil or tyvaso or remodulin Or MeSH descriptor: [Iloprost] or caverject or edex or f5td010360 or lipo pge1 or lipo-pge1 or minprog or muse or pge1 or pge1alpha or prostaglandin e1 or prostaglandin e1alpha or prostavasin or prostin vr or prostine vr or sugiran or vasaprostan or viridal OR iloprost or ciloprost or jed5k35ygl or ventavis or zk 36374 or zk-36374 or zk36374 or MeSH descriptor: [Alprostadil] or ciloprost or</p>

	<p>endoprost or ilomedin or ilomedine or sh 401 or sh401 or shl 401 a or shl 401a or shl401a or ventavisor zk 36374 or zk 36375or zk36374 or zk36375 or alista or aloprastadil or alprestil or alprostadil or alprostanor alprostapintor alprostin or alprox or alyprostor befar or bondil or caverject or caverjet or edex or eglandin or femprox or karon or lyple or minprog or muse or pg e1 or pge 1 or pge1 or pridax or prink or promostan or prostaglandin e 1 or prostaglandine e1 or prostin or prostine vr or prostivas or topiglan or vasostenoon or virirec or vitaros or vytaros or prostavasin or sugiran or vasaprostan or viridal or MeSH descriptor: [Respiratory Distress Syndrome] explode all trees</p> <p>AND</p> <p>ards ((adult or acute or idiopathic) NEAR/2 respiratory distress) Or MeSH descriptor: [Respiratory Distress Syndrome] explode all trees or "shock lung" or "stiff lung" Or MeSH descriptor: [Acute Lung Injury] explode all trees or MeSH descriptor: [Ventilator-Induced Lung Injury] explode all trees OR MeSH descriptor: [Respiratory Insufficiency] explode all trees or MeSH descriptor: [Pulmonary Edema] explode all trees or MeSH descriptor: [Pneumonia] explode all trees</p> <p>AND</p> <p>MeSH descriptor: [Mortality] explode all trees or MeSH descriptor: [Mortality] explode all trees or MeSH descriptor: [Survival Analysis] explode all trees MeSH descriptor: [Quality of Life] explode all trees or MeSH descriptor: [Quality of Life] explode all trees OR MeSH descriptor: [Pain] explode all trees OR MeSH descriptor: [Health] explode all trees Or MeSH descriptor: [Health Status Indicators] explode all trees Or MeSH descriptor: [Health Status] explode all trees Or respond* or response* or failure* or mortality or fatal* or death or dead or deaths Or regress* or surviv* or nonsurviv* or cure or cures or "quality of life" or "qol" or HRQL or "life quality" or morbidit* or adverse or "side effect* side effects" or event or events or nausea or nauseous or vomit* or emesis or comfort* or pain or painful or painfree or stress or analges* Or MeSH descriptor: [Oxygen] explode all trees and with qualifier(s): [blood - BL] or oxygenation</p>
<p>Scopus (via Elsevier)</p>	<p>(((TITLE-ABS-KEY (respiratory AND distress AND syndrome OR ards OR acute AND lung AND injury OR ventilator-induced AND lung AND injury)) OR (TITLE-ABS-KEY ((shock AND lung OR stiff AND lung))) OR (TITLE-ABS ((vili OR ards))) OR (TITLE-ABS-KEY ((pulmonary OR respiratory) W/2 ("distress syndrome"))) OR (TITLE-ABS-KEY ((acute OR chronic) W/2 (lung OR respiratory) W/2 (insufficiency OR failure))))))</p> <p>AND</p> <p>(((TITLE-ABS-KEY ((prostaglandin* OR pgi2 OR pgx OR "prostaglandin i 2" OR "prostaglandin I2" OR "prostaglandin x" OR "u 53217"))) OR (TITLE-ABS-KEY ((prostacyclin* OR epoprostenol OR 35121-78-9 OR pgi2 OR pgx OR "prostaglandin i 2" OR "prostaglandin I2" OR "prostaglandin x" OR treprostini))) OR (TITLE-ABS-KEY ((15au81 OR bw15au OR "hexadecyl treprostini" OR ins1009 OR lrx15 OR orenitram OR remodulin OR trepulumix OR tyvaso OR u62840 OR uniprost OR ut15 OR ut15c OR iloprost OR ciloprost OR endoprost OR ilomedin OR ilomedine OR sh401 OR shl401a OR zk36374 OR zk36375))) OR (TITLE-ABS-KEY ((745-65-3 OR alista OR aloprastadil OR alprestil OR alprostadil OR</p>

or ut 15c or us15 or uc15c or iloprost or iloprost or cicoprost or endoprost or ilomedin or ilomedin or sh 401 or s1401 or shl 401 a or shl 4010 or scl40a1 or ventavis zk 3637c or zk 3637506 z33634 or zk36374)

AND

TS=((Outcome NEAR/2 (measure* or assess*))) OR TS=(mortality or survival analysis or survival or pain measurement or pain or health status or health or health status indicator) OR TS=(response* or respond* or failure* or mortality or fatal* or death or dead or deaths) OR TS=("passed away" or demise* or recurren* or progression or progressed or relaps* or growth or grew or growing)) OR TS=((regress* or surviv* or nonsurviv* or cure or cures or "quality of life")) OR TI(("qol" or HRQL or "life quality")) OR TS=((morbidit* or adverse or "side effect" or "side effects" or event or events or nausea or nauseous or vomit* or emesis or comfort or pain or painful or painfree or stress or analges*)) OR TS=((oxygen NEAR/2 blood) or blood oxygenation)

NOT

TS=(case NEAR/1 report*)

Table S2. PRISMA 2020 Checklist.

Section and Topic	Item #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review.	1 (title page)
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2 (abstract)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4 (last paragraph)
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5 (1 st paragraph)
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5 (2 nd paragraph)
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5 (1 st paragraph)
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplement (Table S1)
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5 (2 nd paragraph)
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6 (1 st paragraph)
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6 (1 st paragraph)
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6 (1 st paragraph)
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6 (2 nd paragraph)
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7 (1 st paragraph)
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7 (1 st paragraph)

Section and Topic	Item #	Checklist item	Reported on page #
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7 (1 st paragraph)
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7 (1 st paragraph)
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7 (1 st paragraph)
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	7 (1 st paragraph)
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	7 (1 st paragraph)
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	6 (2 nd paragraph)
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	6 (3 rd paragraph)
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplement (Table S3)
Study characteristics	17	Cite each included study and present its characteristics.	Supplement (Table S4)
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplement (Table S5)
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supplement (Table S4)
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supplement (Table S6)
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8 (3 rd paragraph) Figure 2, 3 4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Figure 2, 3 4
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Figure 2, 3

Section and Topic	Item #	Checklist item	Reported on page #
			4
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Figure 2, 3 4
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Figure 2, 3 4
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	8 (3 rd paragraph)
	23b	Discuss any limitations of the evidence included in the review.	10 (2 nd paragraph)
	23c	Discuss any limitations of the review processes used.	10 (2 nd paragraph)
	23d	Discuss implications of the results for practice, policy, and future research.	10 (3 rd paragraph)
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5 (2 nd paragraph)
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5 (2 nd paragraph)
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	5 (2 nd paragraph)
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	1 (title page)
Competing interests	26	Declare any competing interests of review authors.	1 (title page)
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	5 (2 nd paragraph)

Table S3. Excluded full-text articles and rationale for exclusion

	Trial	Reason for exclusion
1	Bihari D, Smithies M, Gimson A, Tinker J. The effects of vasodilation with prostacyclin on oxygen delivery and uptake in critically ill patients. <i>N Engl J Med.</i> 1987; 317(7):397-4013.	PaO ₂ /FiO ₂ not reported
2	Silverman HJ, Slotman G, Bone RC, et al. Effects of prostaglandin E ₁ on oxygen delivery and consumption in patients with the adult respiratory distress syndrome: results from the prostaglandin E ₁ multicenter trial. <i>Chest.</i> 1990; 98:405-410.	PaO ₂ /FiO ₂ not reported
3	Zwissler B, Kemming G, Habler O, et al. Inhaled prostacyclin (PGI ₂) versus inhaled nitric oxide in adult respiratory distress syndrome. <i>Am J Respir Crit Care Med.</i> 1996; 154:1671-1677.	Less than 10 patients
5	Bein T, Metz C, Keyl C, et al. Cardiovascular and pulmonary effects of aerosolized prostacyclin administration in severe respiratory failure using a ventilator nebulization system. <i>J Cardiovasc Pharmacol.</i> 1996; 27(4):583-586.	Less than 10 patients
6	Putensen C, Hormann C, Kleinsasser A, Putensen-Himmer G. Cardiopulmonary effects of aerosolized prostaglandin E ₁ and nitric oxide inhalation in patients with acute respiratory distress syndrome. <i>Am J Respir Crit Care Med.</i> 1998; 157:1743-1747.	PaO ₂ /FiO ₂ not reported
7	van Heerden PV, Barden A, Michalopoulos N, et al. Dose-response to inhaled aerosolized prostacyclin for hypoxemia due to ARDS. <i>Chest.</i> 2000; 117: 819-827.	Less than 10 patients
8	Peter M, Jaffe B, Gilbert C, Baram M. Effect of inhaled epoprostenol on oxygenation, outcome, and diuresis in critically ill patients. <i>Chest.</i> 2011; 140:287A.	PaO ₂ /FiO ₂ not reported
9	Scoville BA, Tan P, Johnson DW, Aaronson P. Comparison of short-term pulmonary improvement associated with inhaled nitric oxide and inhaled epoprostenol for acute respiratory distress syndrome. <i>Pharmacotherapy.</i> 2011; 31:324e.	PaO ₂ /FiO ₂ not reported

10	McMillen J, Krumenacker L, Faircloth B, Rowe A. Effect of low dose corticosteroids on response to inhaled epoprostenol in patients with septic shock and ARDS. <i>Crit Care Med.</i> 2012; 40(12):1-328.	PaO ₂ /FiO ₂ not reported
11	Ross B, Miller M, Oliveira P. A retrospective comparison of an inhaled epoprostenol dosing protocol versus conventional therapy with inhaled nitric oxide on outcomes in patients with severe acute respiratory distress syndrome. <i>Crit Care Med.</i> 2012; 40(12):1-328.	PaO ₂ /FiO ₂ not reported
12	Mullin R, Lam S, Conci D, Heresi G, Sasidhar M. Inhaled aerosolized prostacyclin as an efficacious and economic alternative to inhaled nitric oxide. <i>Chest.</i> 2012; 142(4):401A.	PaO ₂ /FiO ₂ not reported
13	Trongtrakul K, Wongs A, Piyawechvirutana K. Effects of inhaled nitroglycerin compared with inhaled iloprost in patients with hypoxemic acute respiratory distress syndrome. <i>Intensive Care Medicine.</i> 2013; 0135: S247.	PaO ₂ /FiO ₂ not reported
14	Aboeed A, Manickavel S, Mathew JJ, Africano J, Khan MA. Comparison of inhaled nitric oxide with epoprostenol in hypoxic respiratory failure. 2014; <i>Am J Respir Crit Care Med.</i> 189: A4473.	PaO ₂ /FiO ₂ not reported
15	Wiedmar J, Kim A, Deibel K. Pharmacoeconomic analysis of inhaled epoprostenol vs nitric oxide for severe, refractory ARDS. <i>Crit Care Med.</i> 2014; 42(12): A1514-A1515.	Less than 10 patients
16	Gayed R, Aslami M, Rabinovich M, Jacobs S, George D, Honig E. Clinical and economic outcomes of inhaled epoprostenol versus nitric oxide for refractory hypoxemia. <i>Crit Care Med.</i> 2016; 44(12): 336.	PaO ₂ /FiO ₂ not reported
17	Lopez N, Siu C, Lin H. Comparison of inhaled epoprostenol products in acute respiratory distress syndrome. <i>Crit Care Med.</i> 2016; 44(12): 334.	PaO ₂ /FiO ₂ not reported
18	Newsome AS, Sultan S, Murray B, et al. Effect of inhaled iloprost on gas exchange in inhalation injury. <i>Burns Open.</i> 20017; 1:49-53.	Less than 10 patients

19	Payne S, Yeung SYA, Gonzales J. Inhaled epoprostenol for the management of hypoxic respiratory failure in an intensive care unit. <i>Crit Care Med.</i> 2017; 46(1): 949.	PaO ₂ /FiO ₂ not reported
20	Bernardo R, Jaliawala H, Brown B. The use of aerosolized prostacyclins is associated with improvements in gas-exchange but no difference in hemodynamics in critically-ill patients. <i>Eur Respir J.</i> 2018; 52: PA2315.	PaO ₂ /FiO ₂ not reported
21	Hussain S, Jaliawala HA, Tsui J, Brown BR, Bernardo RJ. Use of aerosolized prostacyclins in critically ill patients an association with clinical outcomes. <i>Am J Respir Crit Care Med.</i> 2019; 199: A5068.	PaO ₂ /FiO ₂ not reported
22	Bellfi L, Costello P, Bastow S, Bullard H, Miller MK, Sokol S. Inhaled epoprostenol versus inhaled nitric oxide in acute respiratory distress syndrome. <i>Crit Care Med.</i> 2019; 47(1): 534.	PaO ₂ /FiO ₂ not reported
23	Bernardo R, Hussain S, Jaliawala H, Brown B. Predictors of improvement in gas exchange in patients receiving aerosolized iloprost. <i>Crit Care Med.</i> 2019; 47(1): 559.	PaO ₂ /FiO ₂ not reported
24	Jaber J, Reddy R, Hyde R, Parikh S, Urbine D, Kalra S. Overuse of aerosolized prostacyclin in the management of ARDS. <i>Chest.</i> 2020; 158(4): A643.	PaO ₂ /FiO ₂ not reported
25	Zhao Z, Yeats J, O'Farrell B, Dhadwal K, Banerjee T, Adlakha A. The use of inhaled iloprost in COVID-19 ARDS patients: an observational study at the Royal Free Hospital. <i>ICMx.</i> 2020; 8(2): 001238.	PaO ₂ /FiO ₂ not reported
26	Ford HJ, Anderson WH, Wendlandt B, et al. Randomized, placebo-controlled trial of inhaled treprostinil for patients at risk of acute respiratory distress syndrome. <i>Ann Am Thorac Soc.</i> 2021; 18(4):641-647.	Less than 10 patients
27	Ammar M, Gu S, Jiang W, et al. Evaluation of aerosolized epoprostenol in COVID-19 ARDS patients. <i>Crit Care Med.</i> 2021; 49(1): 5.	PaO ₂ /FiO ₂ not reported

28	Hon S, HonShideler C, Simmons-Beck R, et al. Inhaled epoprostenol effects on SpO ₂ /FiO ₂ ratios and survival in COVID-19 and non-COVID-19 acute respiratory distress syndrome. <i>Am J Respir Crit Care Med.</i> 2022; 205:A2922.	PaO ₂ /FiO ₂ not reported
29	Matthews L, Baker L, Ferrari M, et al. Compassionate use of pulmonary vasodilators in acute severe hypoxic respiratory failure due to COVID-19. <i>J Intensive Care Med.</i> 2022; 37(8):1101-1111.	PaO ₂ /FiO ₂ not reported
30	Diep U, Tran N, Ferguson K, et al. Evaluation of outcomes with inhaled epoprostenol in nonintubated ICU patients with COVID-19. <i>Crit Care Med.</i> 2022; 50(1):456.	PaO ₂ /FiO ₂ not reported
31	Dittman K, Michelson AP, Kollef MH. Effect of inhaled epoprostenol on P/F ratio in COVID acute respiratory distress syndrome. <i>Am J Respir Crit Care Med.</i> 2022; 205:A5538.	PaO ₂ /FiO ₂ not reported
32	Molineros C, Louzon P, Ventura D, et al. Nebulized treprostinil in pulmonary hypertension or acute respiratory distress syndrome. <i>Crit Care Med.</i> 2022; 50(1):554.	PaO ₂ /FiO ₂ not reported
33	Pino ME, Bessette KM, Sharofi S, et al. Utilizing combination therapy with inhaled epoprostenol and loop diuretics in acute hypoxic respiratory failure from COVID-19. <i>Chest.</i> 2022; 162(4):A714.	PaO ₂ /FiO ₂ not reported
34	Toomey D, O'Brien M, Hayes BD, Wilcox S. A retrospective review of implementation of an inhaled epoprostenol protocol in the emergency department. <i>Am J Emerg Med.</i> 2022; 58:210-214.	PaO ₂ /FiO ₂ not reported
35	Kataria V, Ryman K, Tsai-Nguyen G, et al. Evaluation of aerosolized epoprostenol for hypoxemia in non-intubated patients with coronavirus disease 2019. <i>Hosp Pract.</i> 2022; 50(2):118-123.	PaO ₂ /FiO ₂ not reported
36	Strauser B, Wodtke J. Assessment of the duration of inhaled epoprostenol therapy for the treatment of ARDS due to COVID-19 and associated mortality. <i>J Am Coll Clin Pharm.</i> 2022; 5:729-786.	PaO ₂ /FiO ₂ not reported

37	Khurana N, Thompson A, Duong H, et al. High-flow nasal cannula and inhaled epoprostenol response in COVID-19. <i>Chest</i> . 2022; 162(4):A1122.	PaO ₂ /FiO ₂ not reported
38	Sharma N, Bhagat MK, Dudney TM, et al. Use of inhaled epoprostenol delivered by high-flow nasal cannula in patients with severe acute hypoxemic respiratory failure secondary to COVID-19. <i>Am J Respir Crit Care Med</i> . 2022; 205:A4282.	PaO ₂ /FiO ₂ not reported
39	Krueger C, Malek N, Khandan-Rooshakib H. Evaluation of response rate to fixed dose inhaled epoprostenol. <i>Crit Care Med</i> . 2023; 51(1):366.	PaO ₂ /FiO ₂ not reported
40	Ochogbu O, Delgado C, Carrillo M, Ruiz AL. Comparing outcomes in responders versus nonresponders to inhaled epoprostenol in COVID-19 ARDS. <i>Crit Care Med</i> . 2023; 51(1):389.	PaO ₂ /FiO ₂ not reported
41	Jaliawala HA, Tsui J, Bernardo RJ, et al. Use of aerosolized epoprostenol is associated with improvements in gas exchange and hemodynamics in critically ill patients. <i>Am J Respir Crit Care Med</i> . 2018; 197: A5108.	Standard deviation not reported

Table S4. Characteristics of included trials

Study	Study Design	Patients	Intervention	Therapy Duration	Primary Outcome
1996 Walmrath	Prospective, crossover	-16 adults -ARDS (AECC) -Mean baseline P/F 114±12 mmHg -Mortality 44%	-iEPO (Flolan) 1.5-34 ng/kg/min -Mean dose 7.5±2.5 ng/kg/min -Crossover with iNO	-< 70 minutes	-Change in P/F
1998 Meyer	Prospective, cohort	-15 adults -ALI (P/F < 160) -APACHE II 33±2 -Mean baseline P/F 105±9 mmHg -Mortality 40%	-Alprostadiol -Mean dose 41±2 mcg/h -Range 20-80 mcg/h	-Mean 103±17 h -Range 1-7 days	-Change in P/F

2001 Domenighetti	Prospective, cohort	-15 adults -ARDS (P/F < 150) -SAPS II 62.9±5.0 -Mean baseline P/F 155±15 mmHg -Mortality 43%	-iEPO (Flolan) 2-40 ng/kg/min	-75 min	-Oxygenation -Pulmonary hemodynamics
2005 Camamo	Retrospective, chart review	-27 adults (10 iEPO, 17 alprostadil) -ARDS (AECC) -Mean baseline P/F iEPO 66.7±23 mmHg -Mean baseline P/F alprostadil 106.1±53.4 mmHg -Mortality 67%	-iEPO max dose 34.3±13.2 ng/kg/min -Alprostadil max dose 28.3±14.2 ng/kg/min	-iEPO 5.9±7.6 d -Alprostadil 4.6±3.1 d	-Change in P/F
2009 Raheem	Prospective chart review	-15 adults -ARDS -APACHE II 29 (21-37) -Median baseline P/F: 59 (33-80) -Mortality 33%	-iEPO (dose not mentioned)	-Median duration 23 (1-46) h	-Oxygenation
2012 Tabrizi	Retrospective, chart review	-36 adults -Hypoxemia (P/F < 100) -Mean baseline P/F 66.9±15.77 mmHg -Mortality 61%	-iEPO (Flolan) – dose not reported	-Not reported	-Change in P/F
2013 Torbic	Retrospective, chart review	-105 adults -60% ARDS -APACHE II 18 (15-22) - Mean baseline P/F 241.67±150.57 mmHg	-iEPO (Flolan) 0.01-0.05 mcg/kg/min	-Mean 3.2±2.6 days	-Change in P/F

		-Mortality 49%			
2013 Dunkley	Retrospective, chart review	-16 adults -ARDS (AECC) -Mean baseline P/F 110±20 mmHg -Mortality 56%	-iEPO (Flolan) max dose 50 ng/kg/min	-Mean 4.8±6.0 days	-Change in P/F
2013 Sawheny	Prospective, cohort	-20 adults -ARDS (AECC) and PH -Mean baseline P/F 177±60 mmHg	-Iloprost 10-20 mcg	-2 hours	-Change in PaO2
2013 Siddiqui	Prospective, randomized control trial	-34 adults -ARDS (AECC) -APACHE II 24 (22.82-25.18) -Median baseline P/F 141.15 (120.77-161.53) mmHg	-Alprostadil 20 mcg	-30 min	-Change in LVEDP, P/F and PAP from baseline
2014 Pacheco	Retrospective, chart review	-216 adults -ARDS (Berlin) -APACHE II 15.6±6.2 (survivors); 16.6±5.4 (nonsurvivors) -Mean baseline P/F 94.±34.5 mmHg (survivors); 81.7±32.7 mmHg (nonsurvivors) -Mortality 63%	-iEPO (Flolan) mean dose during 1 st 24h 26.5±10.3 ng/kg/min (survivors); 34.9±12.4 ng/kg/min (nonsurvivors)	-Mean 118.5±85.1 h (survivors); 99.1±108.7 h (nonsurvivors)	-Hospital mortality
2014 Singh	Retrospective, chart review	-98 adults -ARDS (AECC) -APACHE II 19.17±17.27 -Mean baseline P/F 78.93±30.15	-iEPO 20 ng/kg/min	-Not reported	-Efficacy and safety

		-Mortality 50%			
2016 Torbic	Retrospective, chart review	-104 adults -48% ARDS -Mean baseline P/F 241.67±150.57 mmHg (Velettri); 172.66±108.85 mmHg (Flolan) -Mortality 28.8% (Velettri); 49.1% (Flolan)	-iEPO (Flolan/Velettri) 0.01-0.05 mcg/kg/min	-Mean 3.6±3.5 days (Velettri); 3.2±3.6 days (Flolan)	-Change in P/F
2017 Kallet	Retrospective, chart review	-208 adults -ARDS (AECC) -APACHE 26.2±9.0 -Mean baseline P/F 78±37 mmHg -Mortality 56%	-PGI ₂ max dose 50 ng/kg/min	-Not defined	-Responders v. non-responders
2019 Hawn	Retrospective, chart review	-132 adults -ARDS (Berlin) -APACHE III 85.3±31.9 (Flolan), 86.8±33.2 (Velettri) -Mean baseline P/F 79.8±43.7 (Flolan), 93.3±42.7 (Velettri) -Mortality: 71.6% (Flolan), 72.7% (Velettri)	-iEPO (Flolan/Velettri) 0.01-0.05 mcg/kg/min	-Mean 4.0±4.1 days (Flolan); 2.7±3.3 days (Velettri)	-Change in P/F
2020 Degrado	Retrospective, chart review	-38 adults -COVID-19 ARDS -APACHE II 26.9±8.5 -Mean baseline P/F 130±49 mmHg	-iEPO (Flolan/Velettri) 0.01-0.05 mcg/kg/min	-Mean 47.9±58.6 h	-Efficacy and safety

		-Mortality 50%			
2020 Li	Retrospective, chart review	-29 patients -COVID-19 ARDS (P/F<150) -Mean baseline P/F 86.6±28.9 mmHg -Mortality 52% (responders); 81% (nonresponders)	-iEPO (Veletri) 50 ng/kg/min	-Minimum 24 h	-Change in P/F
2021 Buckley	Retrospective, chart review	-139 adults -ARDS (P/F<150) -SOFA 9.6±3.6 -Mean baseline P/F 83.7±27.8 mmHg -Mortality 67.5% (nonresponders); 48.1% (responders)	-iEPO (Veletri) 0.5 mg	-Mean 121.8±407.7 h (non-responders), 75±59.9h (responders)	-Change in P/F at 4h
2021 Sonti	Retrospective, chart review	-80 adults -COVID-19 ARDS -SOFA 12 (11-15) -Median baseline P/F 92(74-122) mmHg -Mortality 60%	-iEPO 50 ng/kg/min	-Not reported	-Change in P/F
2021 Haeberle	Prospective, randomized control trial	-72 adults -COVID-19 ARDS (P/F≤300) -SOFA 10.8±3.7 -Mean baseline P/F 123.2±51.0 mmHg -Mortality 32%	-Iloprost 3 times/day	-5 days	-Change in P/F
2022 Chiles	Retrospective, chart review	-50 adults -COVID-19 ALI -APACHE II 11 (8-14)	-iEPO (generic) 0.01-0.1 mcg/kg/min	-Median 4.3 (2.0-7.3) days	-Responders v. non-responders

Siddiqui 2013	Some concerns	Some concerns	High	High	Some concerns	Some concerns	Some concerns	High
Haeberle 2021	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns

Table S6. Risk of Bias Assessment – Non-Randomized Trials

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	OVERALL BIAS
Walmrath 1996	Low	Low	Low	Low	Low	Low	Low	Low
Meyer 1998	Serious	Moderate	Low	Moderate	Low	Moderate	Low	Moderate
Domenighetti 2001	Low	Low	Low	Low	Low	Low	Low	Low
Camamo 2005	Serious	Moderate	Low	Serious	Low	Low	Low	Serious
Raheem 2009	Serious	Moderate	Low	Serious	Low	Low	Low	Serious
Tabrizi 2012	Serious	Moderate	Low	Serious	Low	Low	Low	Serious
Torbic 2013	Serious	Moderate	Low	Serious	Low	Low	Low	Serious
Dunkley 2013	Serious	Moderate	Low	Serious	Low	Low	Low	Serious
Sawheny 2013	Low	Low	Low	Low	Low	Low	Low	Low
Pacheco 2014	Serious	Moderate	Low	Serious	Low	Low	Low	Serious
Singh 2014	Serious	Moderate	Low	Serious	Low	Low	Low	Serious
Torbic	Serious	Moderate	Low	Serious	Low	Low	Low	Serious

2016								
Kallet 2017	Serious	Moderate	Low	Serious	Low	Low	Low	Serious
Hawn 2019	Serious	Moderate	Low	Serious	Low	Low	Low	Serious
Degrado 2020	Serious	Moderate	Low	Serious	Low	Low	Low	Serious
Li 2020	Serious	Moderate	Low	Serious	Low	Low	Low	Serious
Buckley 2021	Serious	Moderate	Low	Serious	Low	Low	Low	Serious
Sonti 2021	Serious	Moderate	Low	Serious	Low	Low	Low	Serious
Chiles 2022	Serious	Moderate	Low	Serious	Low	Low	Low	Serious
Buckley 2022	Serious	Moderate	Low	Serious	Low	Low	Low	Serious
Imtiaz 2022	Serious	Moderate	Low	Serious	Low	Low	Low	Serious

Table S7. GRADE Quality of Evidence Summary Table.

Quality Assessment						Results	Quality
Number of studies (number of patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		
Change in PaO₂/FiO₂ ratio							
23 (1658)	Serious	Serious ^a	Not serious	Serious ^d	Not serious	MD 40.35 (26.14, 54.56); p<0.00001; I ² =95%	Very low
Change in PaO₂							
8 (354)	Serious	Serious ^b	Not serious	Serious ^d	Not serious	MD 12.68 (2.89, 24.48); p=0.01; I ² =96%	Very low
Change in mPAP							

3 (46)	Serious	Serious ^c	Not serious	Serious ^d	Not serious	MD -3.67 (-5.04, -2.31); p<0.00001; I ² =68%	Very low
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PaO₂: partial pressure of arterial oxygen; FiO₂: fraction of inspired oxygen; mPAP: mean pulmonary artery pressure

^a Unexplained heterogeneity between studies (I²=95%)

^b Unexplained heterogeneity between studies (I²=96%)

^c Unexplained heterogeneity between studies (I²=68%)

^d Confidence interval is such that a different clinical decision might be made depending on where the true value falls

Figure S1. Mean PaO₂/FiO₂ ratio over time

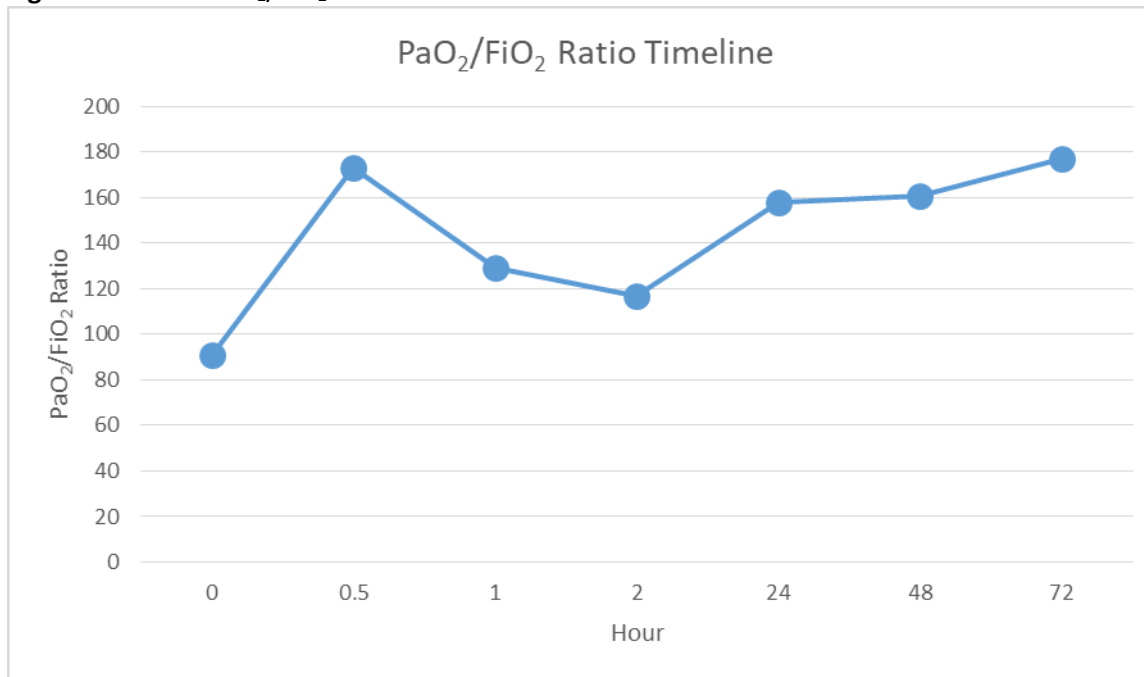


Figure S2. Effect of prostacyclins on PaO₂/FiO₂ ratio in non-COVID-19 ARDS

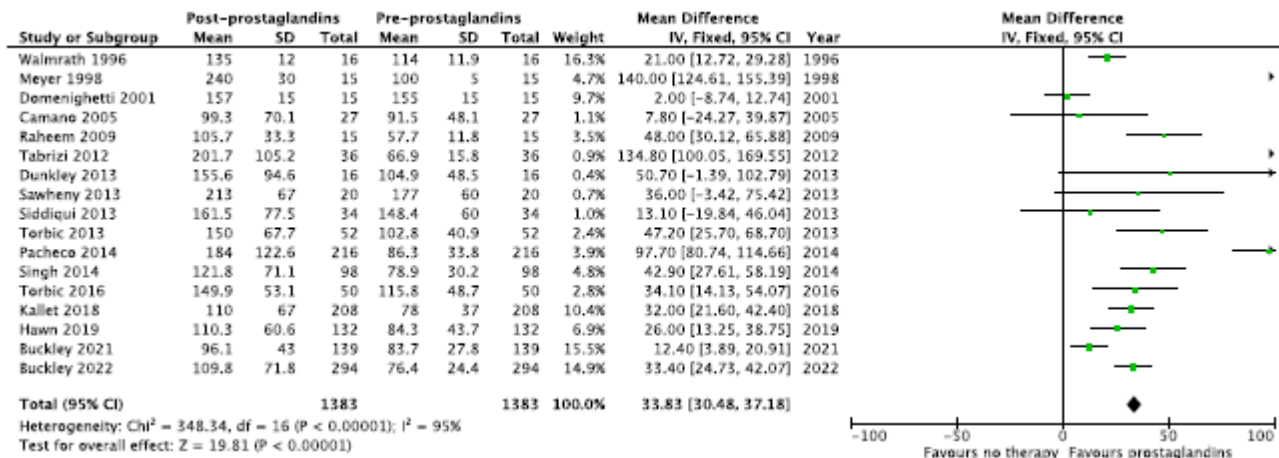


Figure S2. Effect of prostacyclins on PaO₂/FiO₂ ratio in COVID-19 ARDS

