Revisões sistemáticas e metanálise

Prof. Fredi Alexander Diaz Quijano
Departamento Epidemiologia

Revisões sistemáticas

Identificação de estudos já concluídos que abordaram uma questão de pesquisa

e

avaliação dos resultados para se chegar a conclusões sobre um corpo de conhecimentos.

Revisões sistemáticas

Usam uma abordagem bem-definida e uniforme para:

- Identificar todos os estudos relevantes.
- Mostrar os resultados dos estudos elegíveis.
- Quando apropriado, calcular estimativa-sumário.

Metanálise

Métodos estatísticos usados em Revisões sistemáticas para:

- Cálculo das estimativas-sumário de efeito e variância.
- Avaliar a heterogeneidade.
- Avaliar o viés de publicação.

Elementos da Revisão Sistemática

1. Questão de pesquisa clara
2. Identificação abrangente e não-enviesada dos estudos
3. Definição de critérios de inclusão e exclusão
4. Extração uniforme e sem viés das características e dos achados de cada estudo
5. Apresentação clara e uniforme dos dados de estudos individuais.

Questão de pesquisa clara

Em indivíduos admitidos em uma UTI com angina instável,

o tratamento com aspirina mais heparina endovenosa,

reduz o risco de infarto e morte durante hospitalização,

quando comparado ao tratamento apenas com aspirina?

Questão de pesquisa clara

População

Em indivíduos admitidos em uma UTI com angina instável,

Intervenção

o tratamento com aspirina mais heparina endovenosa,

Desfecho

reduz o risco de infarto e morte durante hospitalização,

Grupo de Comparação

quando comparado ao tratamento apenas com aspirina?

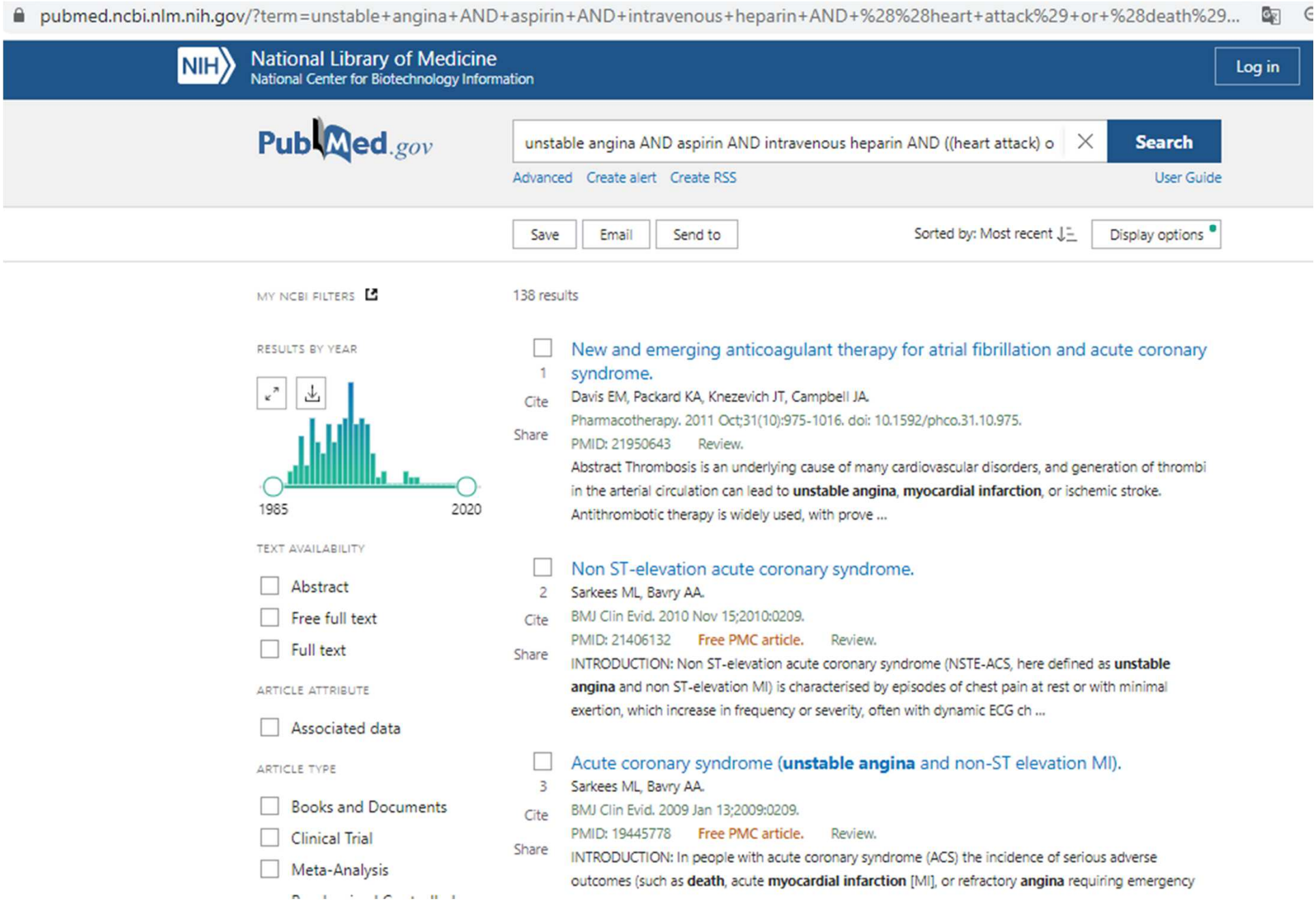
Identificação dos estudos

Termos de Busca:

unstable angina AND aspirin AND intravenous heparin AND ((heart attack) or (death))

As buscas devem incluir várias bases eletrônicas: MEDLINE, EMBASE, Crochrane, etc

Identificação dos estudos



Critérios de inclusão e exclusão dos estudos

Procuram garantir a validade da revisão. Se possível, estabelecidos *a priori*

Tipicamente, referem-se a:

- População
- Doença ou condição de interesse
- Intervenção
- Grupos controle
- Caraterísticas do desenho (cegamento, perdas máximas, duração do seguimento).

Elementos da Revisão Sistemática

1. Questão de pesquisa clara
2. Identificação abrangente e não-enviesada dos estudos
3. Definição de critérios de inclusão e exclusão
4. **Extração uniforme e sem viés das características e dos achados de cada estudo**
5. Apresentação clara e uniforme dos dados de estudos individuais.

Elementos da Revisão Sistemática

1. Questão de pesquisa clara
2. Identificação abrangente e não-enviesada dos estudos
3. Definição de critérios de inclusão e exclusão
4. Extração uniforme e sem viés das características e dos achados de cada estudo
5. **Apresentação clara e uniforme dos dados de estudos individuais.**

Invest Clin 49(1): 111 - 122, 2008

Predictores de sangrado espontáneo en dengue: una revisión sistemática de la literatura.

Fredi Alexander Díaz-Quijano.

combinación de palabras:

Dengue AND (patients OR children OR adult) AND (bleeding OR hemorrhage OR hemorrhages OR metrorrhagia OR hematuria OR hematemesis OR epistaxis OR gingival OR melena OR tourniquet OR Petechiae OR purpura OR Hematochezia) AND (clinical OR manifestation OR laboratory OR test OR platelet OR coagulation OR biochemical OR prognosis OR predict OR associat* OR relation* OR risk).*

OPEN ACCESS Freely available online

PLoS MEDICINE

Guidelines and Guidance

Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

David Moher[1,2]*, Alessandro Liberati[3,4], Jennifer Tetzlaff[1], Douglas G. Altman[5], The PRISMA Group[¶]

1 Ottawa Methods Centre, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada, **2** Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada, **3** Università di Modena e Reggio Emilia, Modena, Italy, **4** Centro Cochrane Italiano, Istituto Ricerche Farmacologiche Mario Negri, Milan, Italy, **5** Centre for Statistics in Medicine, University of Oxford, Oxford, United Kingdom

https://journals.plos.org/plosmedicine/article/file?id=10.1371/journal.pmed.1000097&type=printable

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	

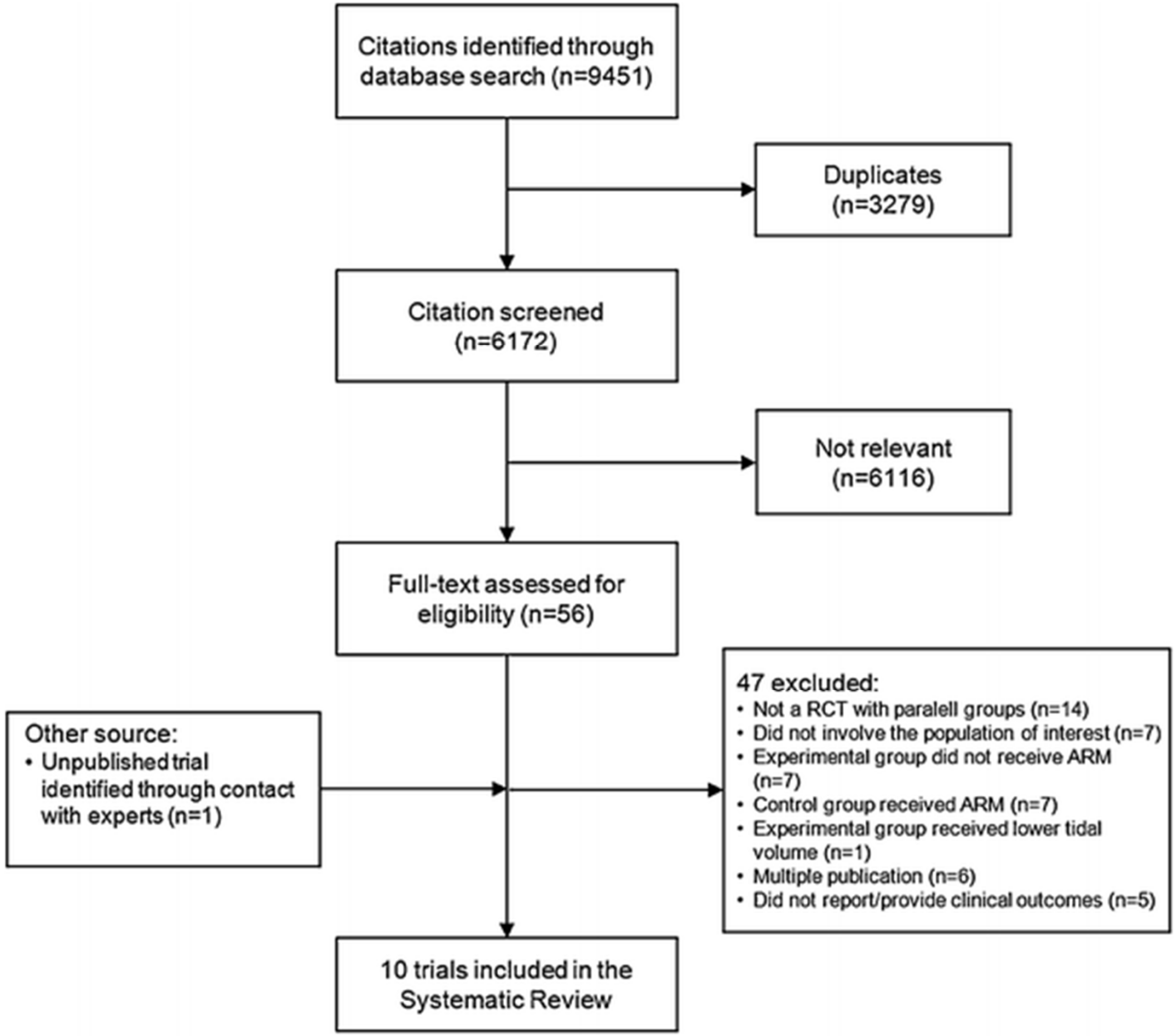
Intensive Care Med (2014) 40:1227–1240
DOI 10.1007/s00134-014-3413-6

SYSTEMATIC REVIEW

Erica Aranha Suzumura
Mabel Figueiró
Karina Normilio-Silva
Lígia Laranjeira
Claudia Oliveira
Anna Maria Buehler
Diogo Bugano
Marcelo Britto Passos Amato
Carlos Roberto Ribeiro Carvalho
Otavio Berwanger
Alexandre Biasi Cavalcanti

Effects of alveolar recruitment maneuvers on clinical outcomes in patients with acute respiratory distress syndrome: a systematic review and meta-analysis


PEEP ALTA
ALVÉOLO



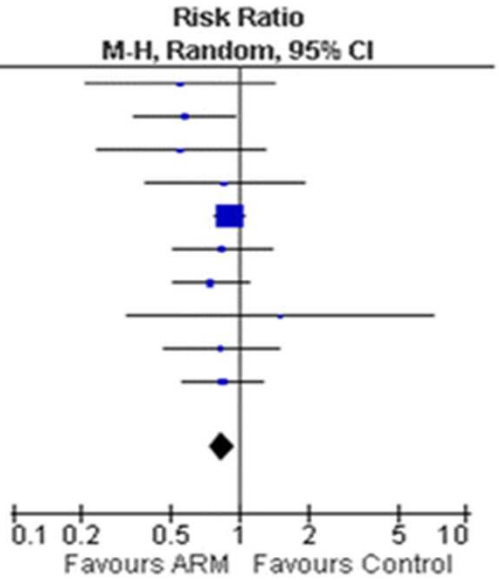
Suzumura EA, et al. Intensive Care Med. 2014 Sep;40(9):1227.

First author/year	Eligibility	Group	Number of patients	Type of ARM	Method to adjustPEEP
Lim/2003 [27]	PaO_2/FiO_2≤200 mmHg for <7 days	ARM	20	Stepwise increase ofPEEP (from 10 to 30 cmH_2O) with a …	PEEP set at 15 cmH_2O for all patients
		Control	8	NA	Similar to experimental group
Park/2003 [28]	PaO_2/FiO_2≤200 mmHg for <2 days	ARM	11	CPAP 30–35 cmH_2O for 30 s, twice daily	PEEP was set before ARM performing stepwise increase from 8 to 15 cmH_2O (in increments of 2 cmH_2O) and set based …
		Control	6	NA	Similar to experimental group
Long/2006 [29]	PaO_2/FiO_2≤200 mmHg for <24 h	ARM	16	Not stated	PEEP was set daily based on P–V curve variation
		Control	14	NA	According to ARDSNet high PEEPtable[b]
Wang/2007 [30]	PaO_2/FiO_2≤200 mmHg	ARM	14	CPAP 35 cmH_2O for 35 s after suctioning	According to ARDSNet table[c]
		Control	14	NA	According to ARDSNet table[c]

Effect on in-hospital mortality

Study or Subgroup	ARM Events	ARM Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Park 2003	4	11	4	6	1.6%	0.55 [0.21, 1.43]	2003
Lim 2003	10	20	7	8	5.7%	0.57 [0.34, 0.95]	2003
Long 2006	5	16	8	14	2.0%	0.55 [0.23, 1.29]	2006
Wang 2007	6	14	7	14	2.3%	0.86 [0.39, 1.91]	2007
Meade 2008	173	475	205	508	58.9%	0.90 [0.77, 1.06]	2008
Huh 2009	14	30	15	27	5.7%	0.84 [0.50, 1.40]	2009
Xi 2010	23	55	31	55	9.8%	0.74 [0.50, 1.09]	2010
Hodgson 2011	3	10	2	10	0.6%	1.50 [0.32, 7.14]	2011
Liu 2011	14	50	17	50	4.3%	0.82 [0.46, 1.48]	2011
Kacmarek 2014	29	99	35	101	9.0%	0.85 [0.56, 1.27]	2014
Total (95% CI)		**780**		**793**	**100.0%**	**0.84 [0.74, 0.95]**	
Total events	281		331				

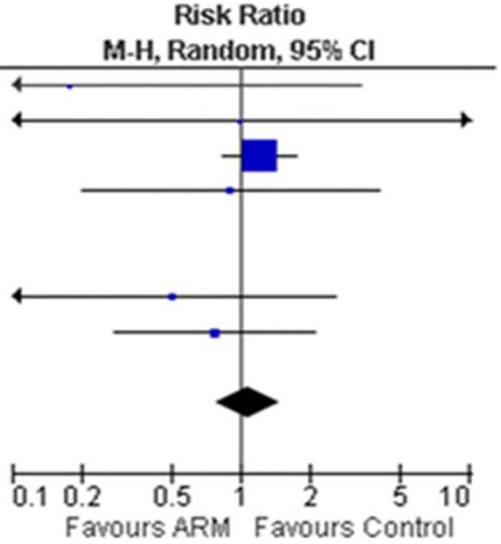
Heterogeneity: Tau² = 0.00; Chi² = 5.71, df = 9 (P = 0.77); I² = 0%
Test for overall effect: Z = 2.86 (P = 0.004)



Effect on barotrauma

Study or Subgroup	ARM Events	ARM Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Long 2006	0	16	2	14	1.2%	0.18 [0.01, 3.39]	2006
Wang 2007	1	14	1	14	1.5%	1.00 [0.07, 14.45]	2007
Meade 2008	53	475	47	508	78.2%	1.21 [0.83, 1.75]	2008
Huh 2009	3	30	3	27	4.7%	0.90 [0.20, 4.09]	2009
Xi 2010	0	55	0	55		Not estimable	2010
Hodgson 2011	0	10	0	10		Not estimable	2011
Liu 2011	2	50	4	50	4.0%	0.50 [0.10, 2.61]	2011
Kacmarek 2014	6	99	8	101	10.4%	0.77 [0.28, 2.13]	2014
Total (95% CI)		**749**		**779**	**100.0%**	**1.07 [0.77, 1.48]**	
Total events	65		65				

Heterogeneity: Tau² = 0.00; Chi² = 3.12, df = 5 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.70)



Effect on severe hypoxemia requiring rescue therapies

Elementos da Revisão Sistemática

(Metanálise)

6. Avaliação da heterogeneidade dos achados dos estudos individuais.
7. Quando apropriado, cálculo de estimativa-sumário do efeito e do Intervalo de confiança.
8. Avaliação do potencial viés de publicação.
9. Análise de subgrupo e de sensibilidade.

Avaliação do heterogeneidade dos estudos

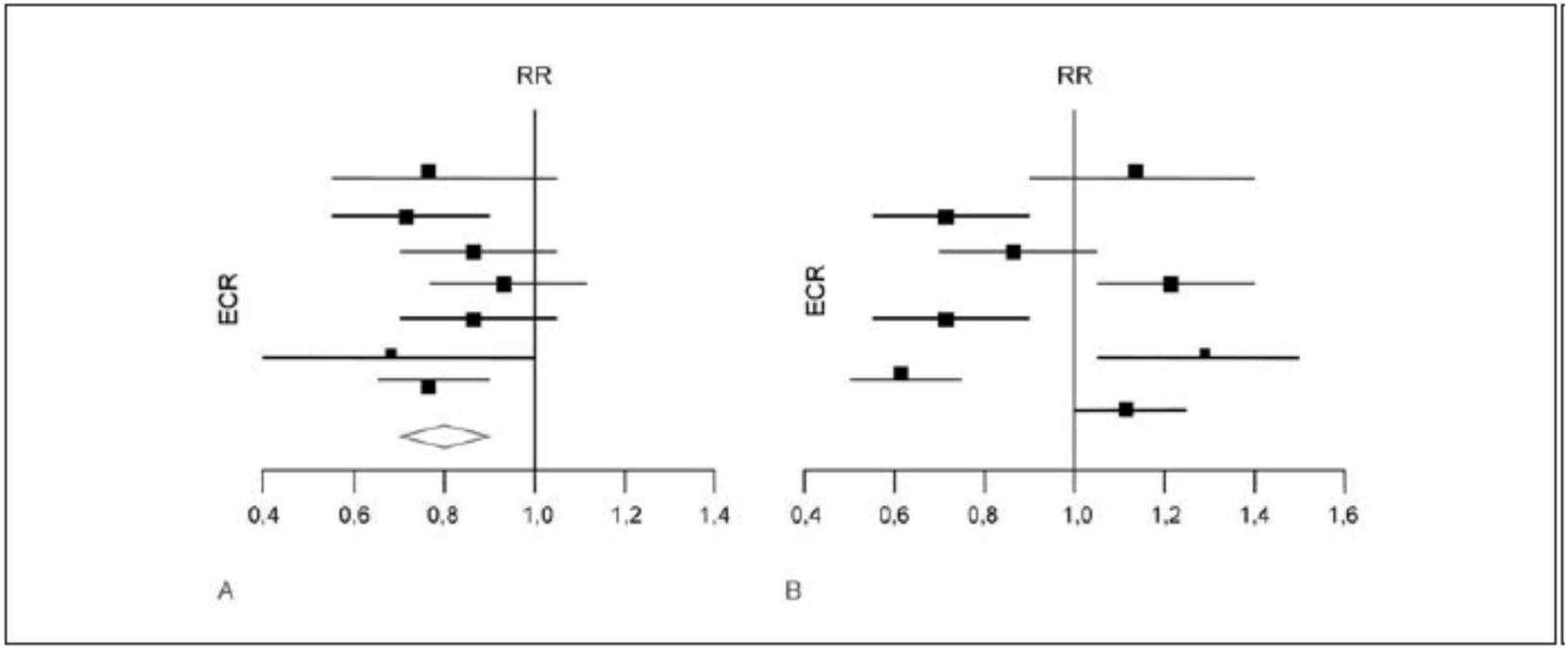


FIGURA 2. Presentación gráfica de ensayos clínicos randomizados (ECR) homogéneos (a izquierda) y heterogéneos (a derecha). RR = riesgo relativo.

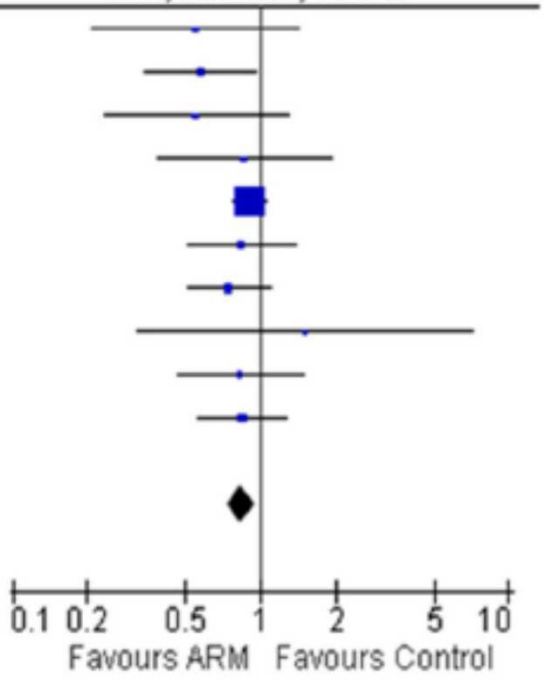
Estimativa sumário e Intervalo de confiança

Effect on in-hospital mortality

Study or Subgroup	ARM Events	ARM Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Park 2003	4	11	4	6	1.6%	0.55 [0.21, 1.43]	2003
Lim 2003	10	20	7	8	5.7%	0.57 [0.34, 0.95]	2003
Long 2006	5	16	8	14	2.0%	0.55 [0.23, 1.29]	2006
Wang 2007	6	14	7	14	2.3%	0.86 [0.39, 1.91]	2007
Meade 2008	173	475	205	508	58.9%	0.90 [0.77, 1.06]	2008
Huh 2009	14	30	15	27	5.7%	0.84 [0.50, 1.40]	2009
Xi 2010	23	55	31	55	9.8%	0.74 [0.50, 1.09]	2010
Hodgson 2011	3	10	2	10	0.6%	1.50 [0.32, 7.14]	2011
Liu 2011	14	50	17	50	4.3%	0.82 [0.46, 1.48]	2011
Kacmarek 2014	29	99	35	101	9.0%	0.85 [0.56, 1.27]	2014
Total (95% CI)		**780**		**793**	**100.0%**	**0.84 [0.74, 0.95]**	
Total events	281		331				

Heterogeneity: Tau² = 0.00; Chi² = 5.71, df = 9 (P = 0.77); I² = 0%

Test for overall effect: Z = 2.86 (P = 0.004)



Suzumura EA, et al. Intensive Care Med. 2014 Sep;40(9):1227.

Estimativa sumário e Intervalo de confiança

Efeito Global (Fixo): $$\hat{\theta} = \frac{\sum_{i=1}^{k} w_i \hat{\theta}_i}{\sum_{i=1}^{k} w_i}$$

$$w_i = \frac{1}{Var(\hat{\theta}_i)}$$

$$Var(\hat{\theta}) = \frac{1}{\sum_{i=1}^{k} w_i}$$

Estimativa sumário e Intervalo de confiança

Se a medida de efeito é o RR, então,

$$\Theta_i = Logaritmo\ natural\ do\ RR$$

$$Var(\Theta_i) = \frac{1}{a} + \frac{1}{c} - \frac{1}{a+b} - \frac{1}{c+d}$$

	Evento	**Nao Evento**	
Expostos	a	b	a+b
Não Expostos	c	d	c+d
	a+c	b+d	n

Estimativa sumário e Intervalo de confiança

Efeito Global (Fixo): $$\hat{\theta} = \frac{\sum_{i=1}^{k} w_i \hat{\theta}_i}{\sum_{i=1}^{k} w_i}$$

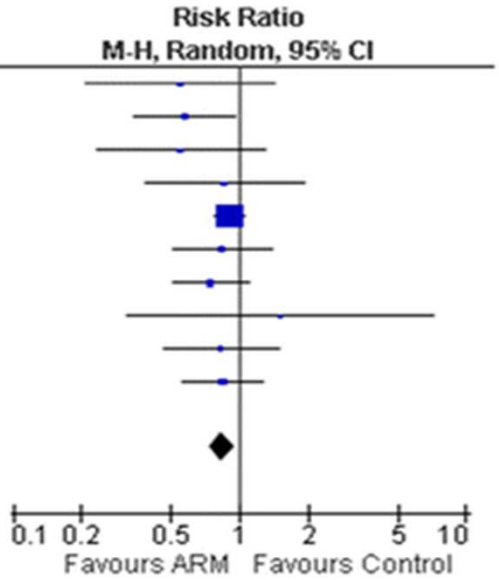
$$w_i = \frac{1}{Var(\hat{\theta}_i)}$$

$$Var(\hat{\theta}) = \frac{1}{\sum_{i=1}^{k} w_i}$$

Effect on in-hospital mortality

Study or Subgroup	ARM Events	ARM Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Park 2003	4	11	4	6	1.6%	0.55 [0.21, 1.43]	2003
Lim 2003	10	20	7	8	5.7%	0.57 [0.34, 0.95]	2003
Long 2006	5	16	8	14	2.0%	0.55 [0.23, 1.29]	2006
Wang 2007	6	14	7	14	2.3%	0.86 [0.39, 1.91]	2007
Meade 2008	173	475	205	508	58.9%	0.90 [0.77, 1.06]	2008
Huh 2009	14	30	15	27	5.7%	0.84 [0.50, 1.40]	2009
Xi 2010	23	55	31	55	9.8%	0.74 [0.50, 1.09]	2010
Hodgson 2011	3	10	2	10	0.6%	1.50 [0.32, 7.14]	2011
Liu 2011	14	50	17	50	4.3%	0.82 [0.46, 1.48]	2011
Kacmarek 2014	29	99	35	101	9.0%	0.85 [0.56, 1.27]	2014
Total (95% CI)		**780**		**793**	**100.0%**	**0.84 [0.74, 0.95]**	
Total events	281		331				

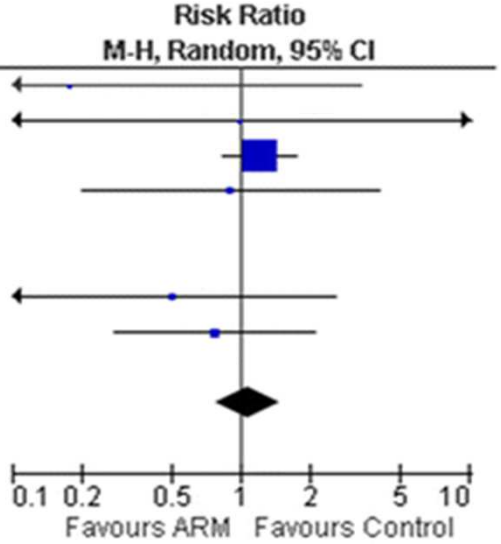
Heterogeneity: Tau² = 0.00; Chi² = 5.71, df = 9 (P = 0.77); I² = 0%
Test for overall effect: Z = 2.86 (P = 0.004)



Effect on barotrauma

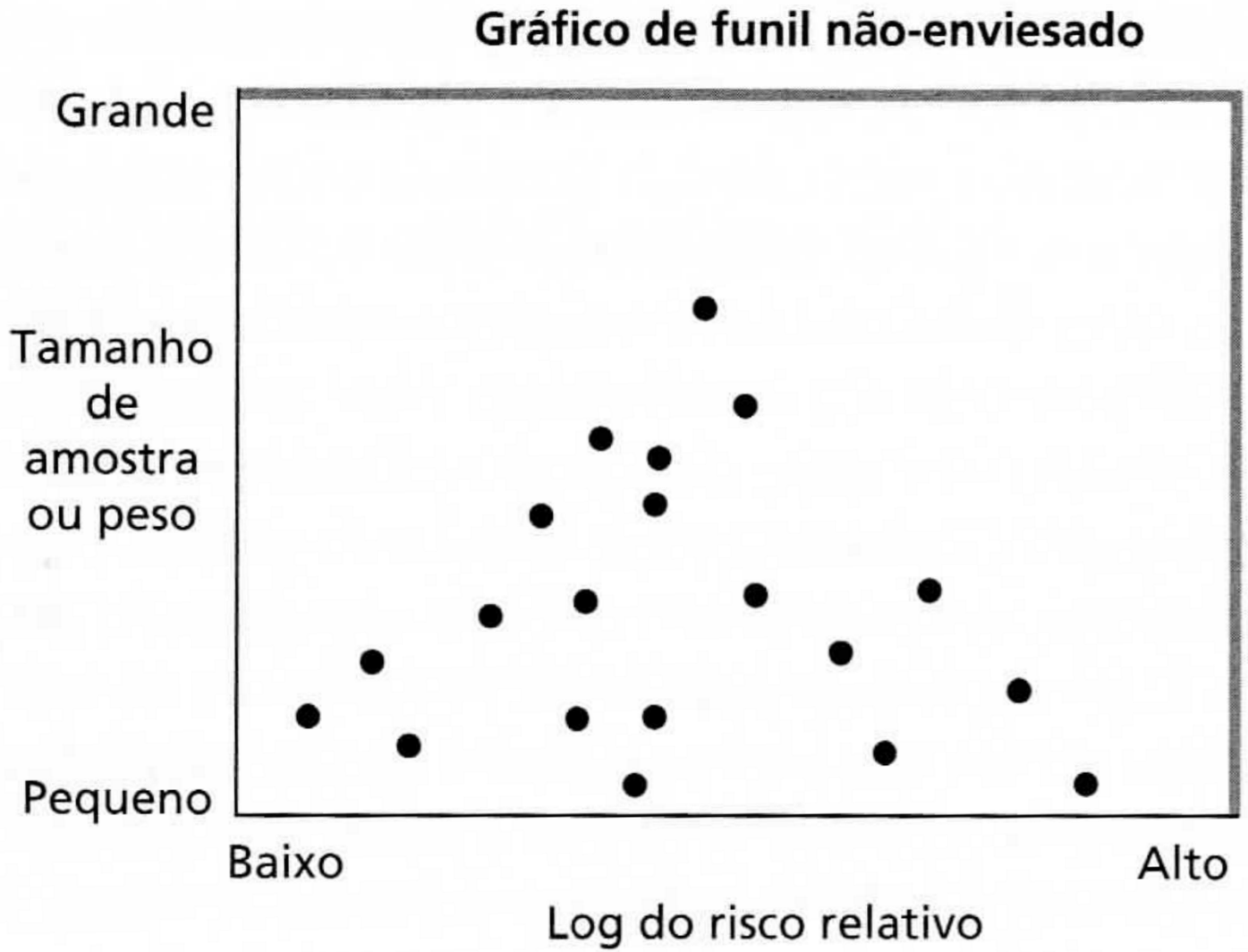
Study or Subgroup	ARM Events	ARM Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Long 2006	0	16	2	14	1.2%	0.18 [0.01, 3.39]	2006
Wang 2007	1	14	1	14	1.5%	1.00 [0.07, 14.45]	2007
Meade 2008	53	475	47	508	78.2%	1.21 [0.83, 1.75]	2008
Huh 2009	3	30	3	27	4.7%	0.90 [0.20, 4.09]	2009
Xi 2010	0	55	0	55		Not estimable	2010
Hodgson 2011	0	10	0	10		Not estimable	2011
Liu 2011	2	50	4	50	4.0%	0.50 [0.10, 2.61]	2011
Kacmarek 2014	6	99	8	101	10.4%	0.77 [0.28, 2.13]	2014
Total (95% CI)		**749**		**779**	**100.0%**	**1.07 [0.77, 1.48]**	
Total events	65		65				

Heterogeneity: Tau² = 0.00; Chi² = 3.12, df = 5 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.70)

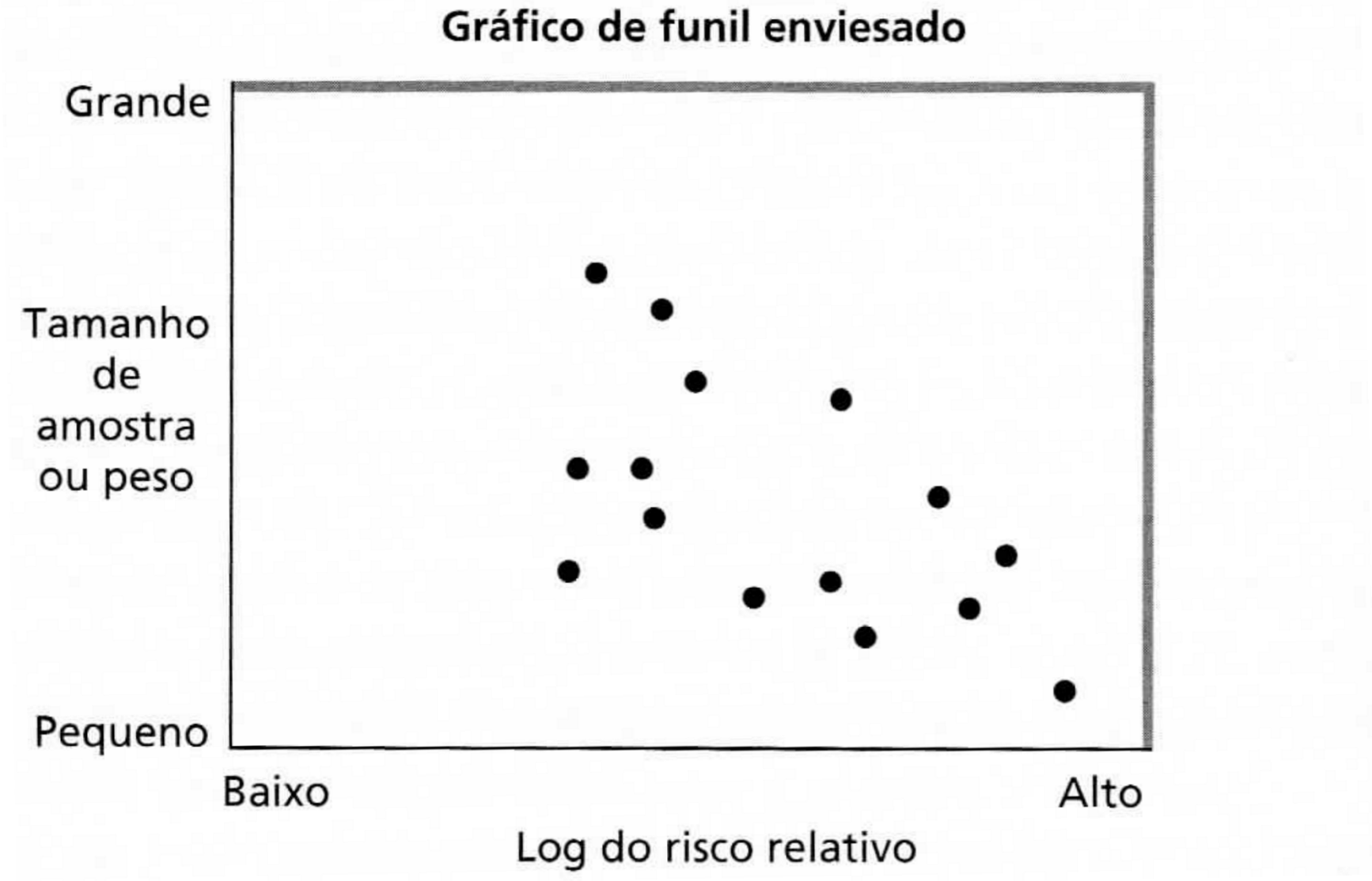


Effect on severe hypoxemia requiring rescue therapies

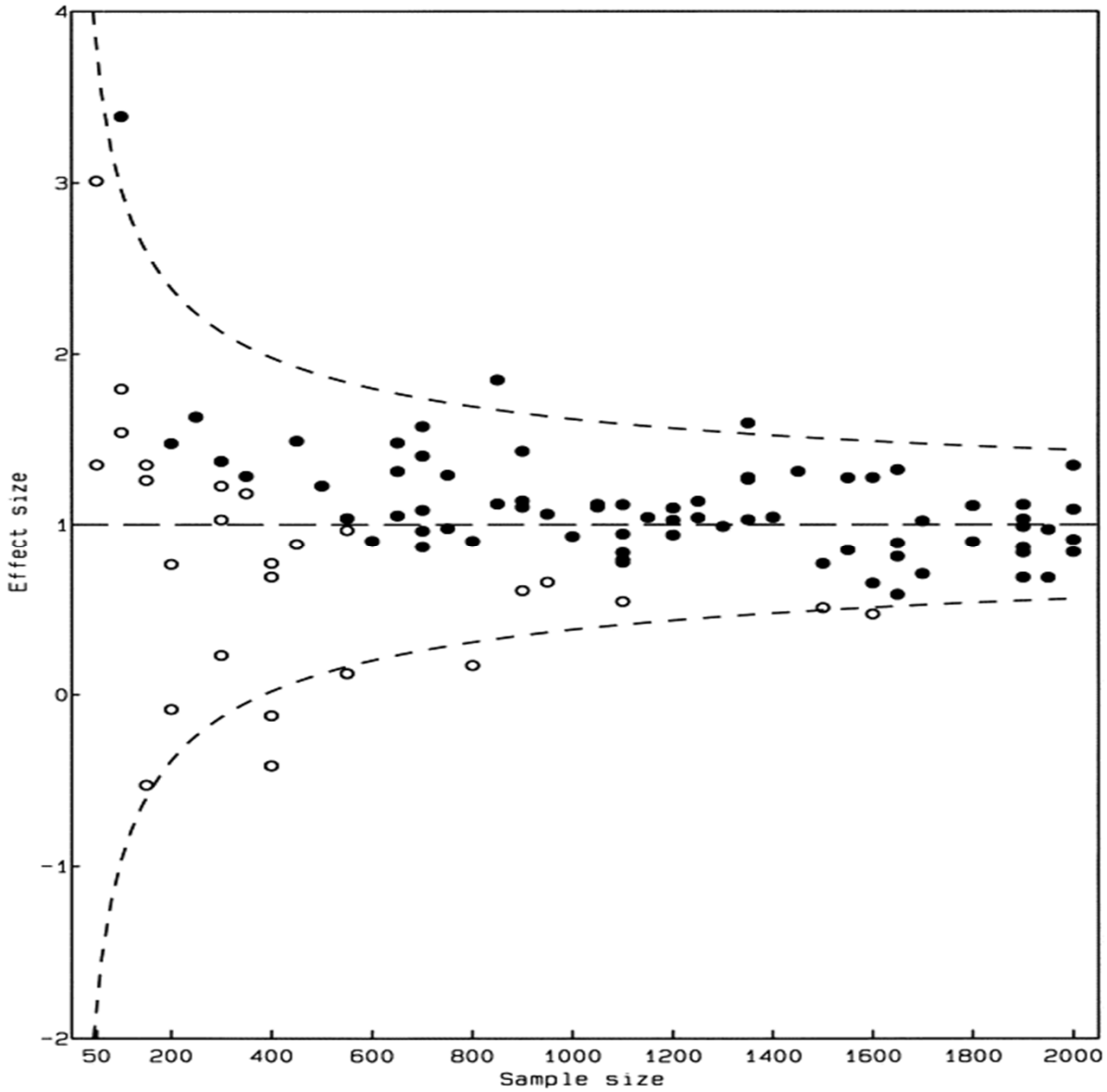
Avaliação do viés de publicação



Avaliação do viés de publicação



Avaliação do viés de publicação

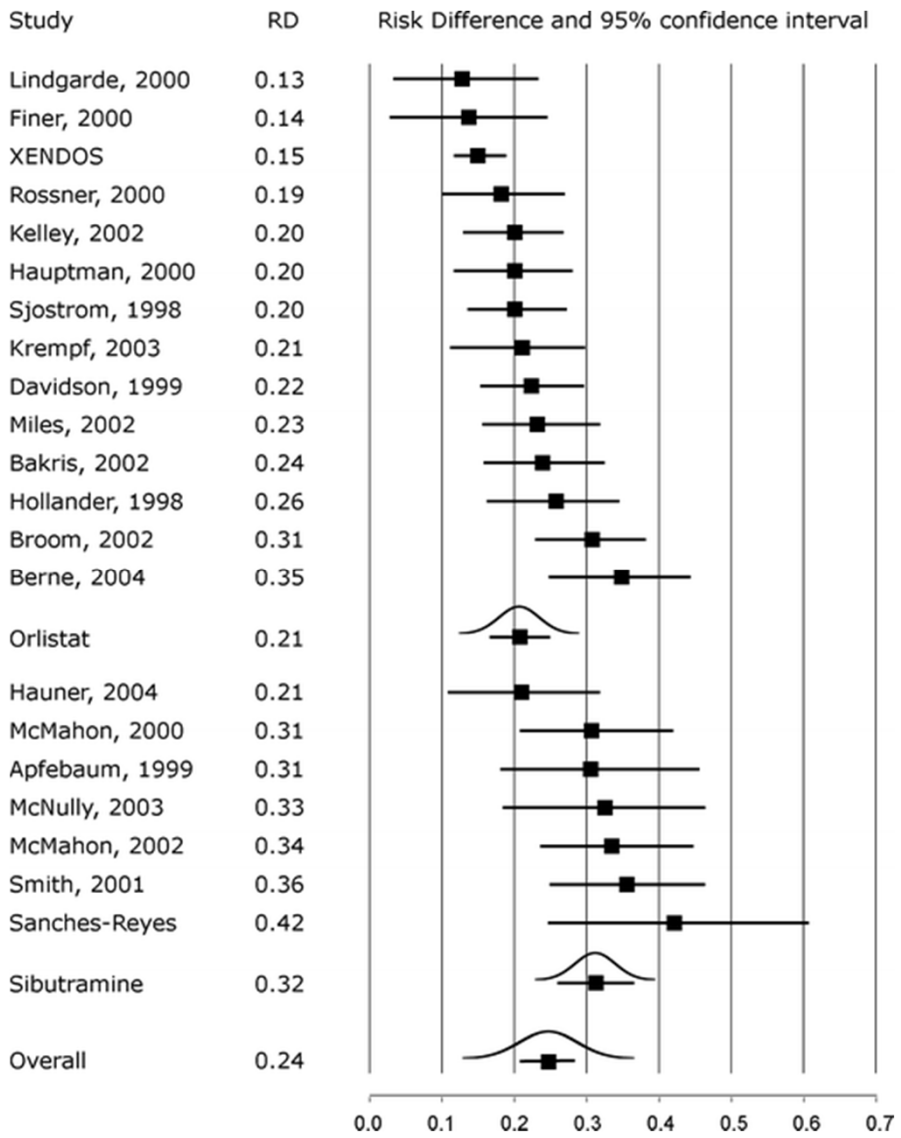


Elementos da Revisão Sistemática

(Metanálise)

6. Avaliação da heterogeneidade dos achados dos estudos individuais.
7. Quando apropriado, cálculo de estimativa-sumário do efeito e do Intervalo de confiança.
8. Avaliação do potencial viés de publicação.
9. Análise de subgrupos e de sensibilidade.

Análise de subgrupos



Análise de sensibilidade.

Avaliação da influência de cada um dos estudos nos resultados.

Replicar a meta-análise excluindo em cada passo um dos estudos incluídos na revisão.

Resultados semelhantes em direção, magnitude do efeito e em significância estatística, indicam um resultado robusto.

Este processo pode ser repetido eliminando vários estudos (Ex, aqueles de pior qualidade, não publicado, etc.) para determinar a sua possível influência nos resultados.

Revisão Sistemática

Importante:

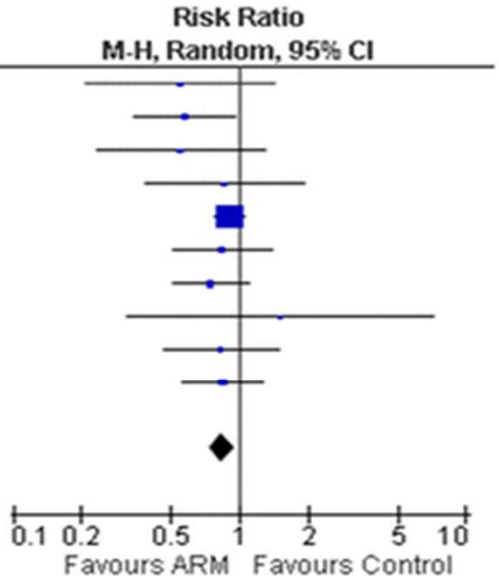
As **características** e os **achados** de estudos individuais devem ser apresentados claramente, permitindo que o leitor forme opiniões que não dependam das estatísticas sumário.

A maior **limitação** da Revisão Sistemática é que a confiabilidade dos resultados é limitada pela qualidade dos estúdios incluídos.

Effect on in-hospital mortality

Study or Subgroup	ARM Events	ARM Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Park 2003	4	11	4	6	1.6%	0.55 [0.21, 1.43]	2003
Lim 2003	10	20	7	8	5.7%	0.57 [0.34, 0.95]	2003
Long 2006	5	16	8	14	2.0%	0.55 [0.23, 1.29]	2006
Wang 2007	6	14	7	14	2.3%	0.86 [0.39, 1.91]	2007
Meade 2008	173	475	205	508	58.9%	0.90 [0.77, 1.06]	2008
Huh 2009	14	30	15	27	5.7%	0.84 [0.50, 1.40]	2009
Xi 2010	23	55	31	55	9.8%	0.74 [0.50, 1.09]	2010
Hodgson 2011	3	10	2	10	0.6%	1.50 [0.32, 7.14]	2011
Liu 2011	14	50	17	50	4.3%	0.82 [0.46, 1.48]	2011
Kacmarek 2014	29	99	35	101	9.0%	0.85 [0.56, 1.27]	2014
Total (95% CI)		**780**		**793**	**100.0%**	**0.84 [0.74, 0.95]**	
Total events	281		331				

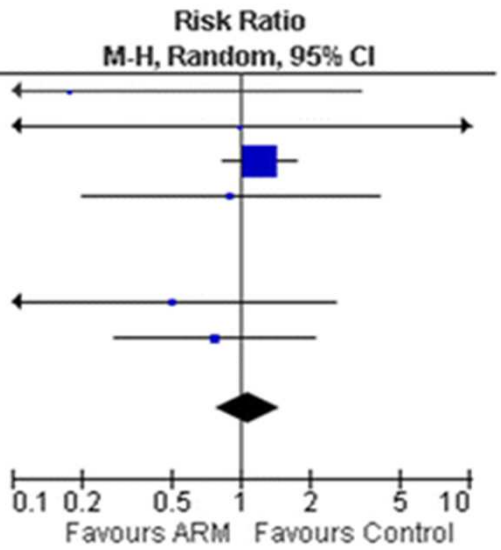
Heterogeneity: Tau² = 0.00; Chi² = 5.71, df = 9 (P = 0.77); I² = 0%
Test for overall effect: Z = 2.86 (P = 0.004)

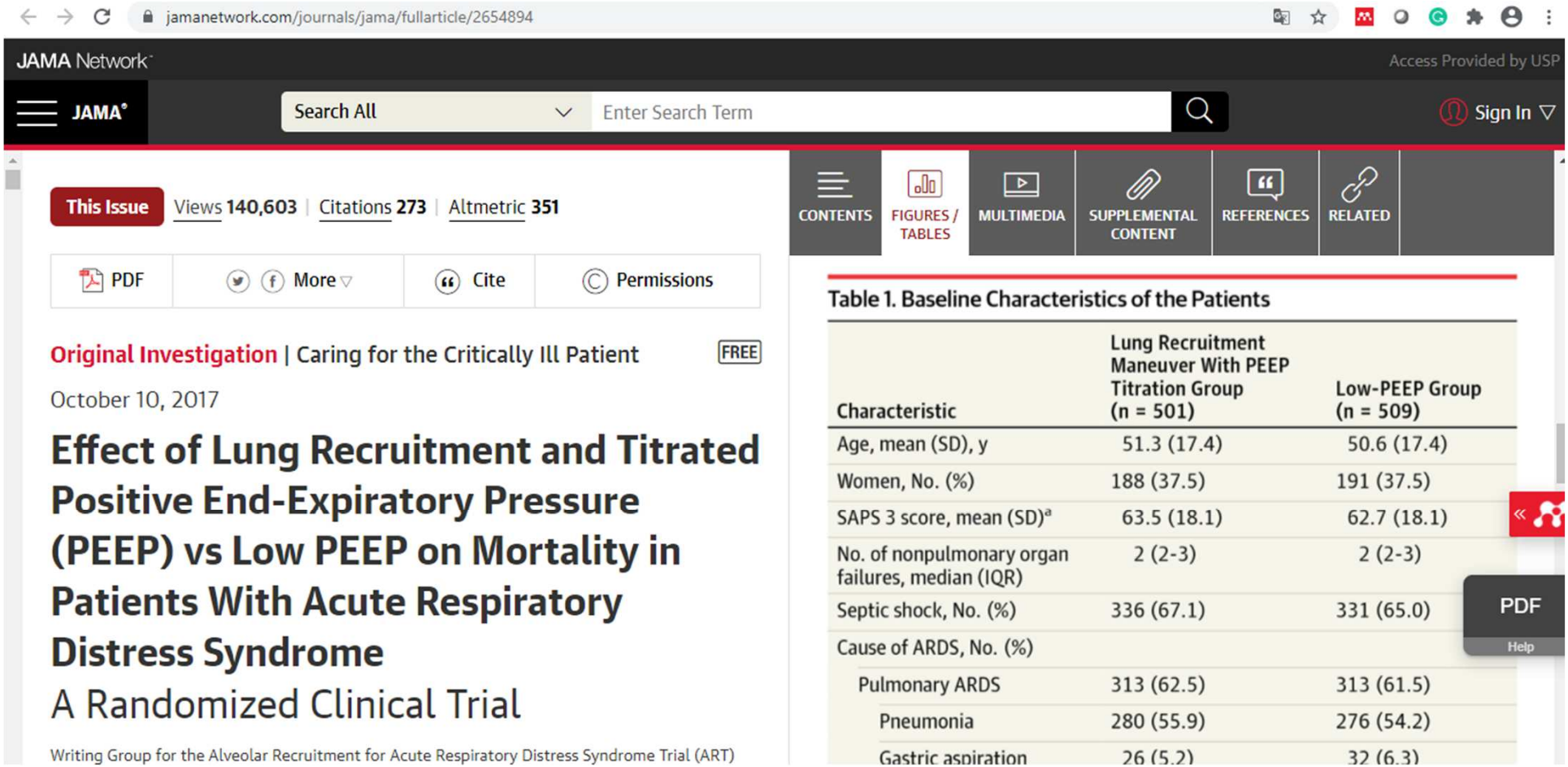


Effect on barotrauma

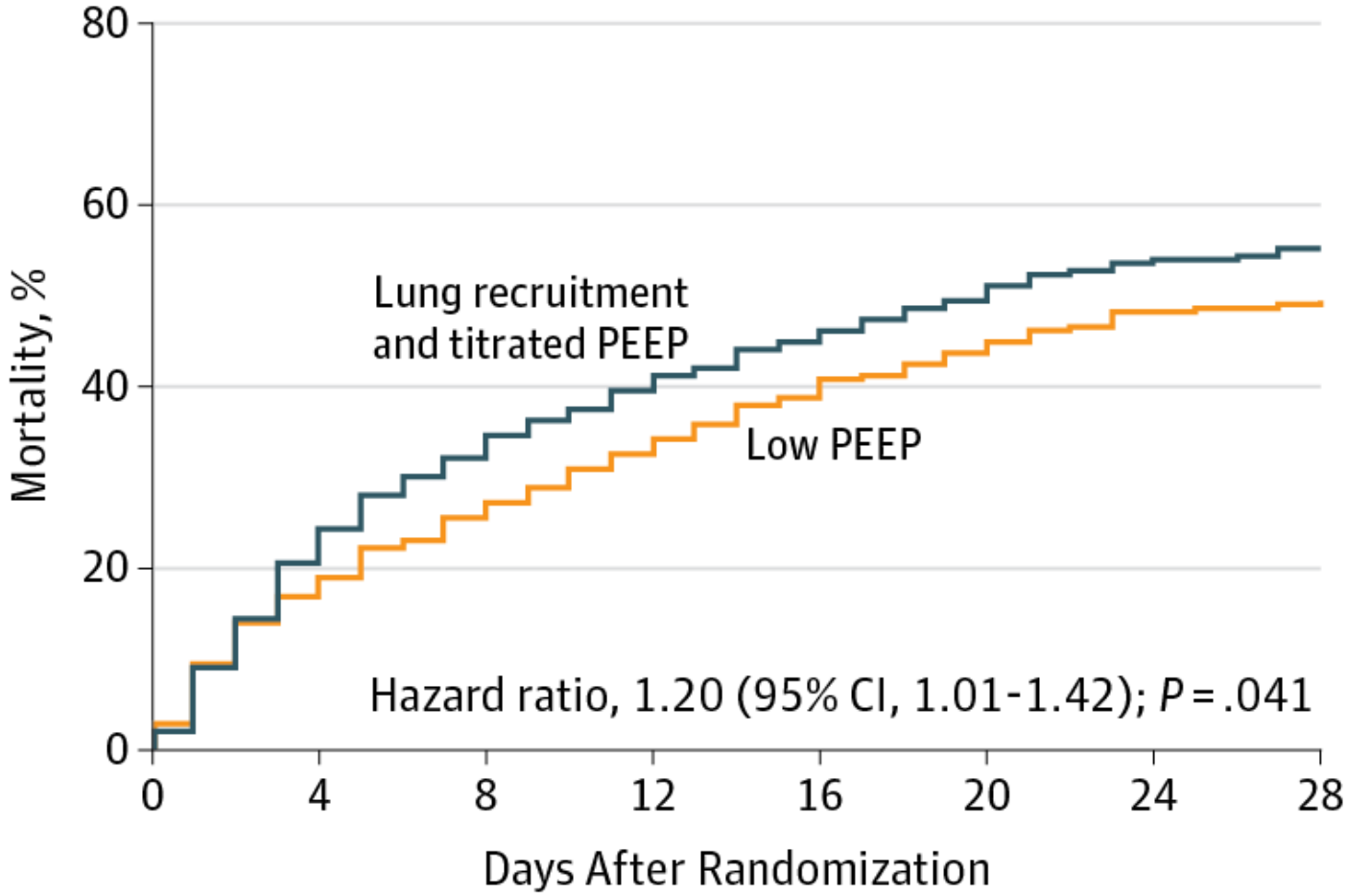
Study or Subgroup	ARM Events	ARM Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Long 2006	0	16	2	14	1.2%	0.18 [0.01, 3.39]	2006
Wang 2007	1	14	1	14	1.5%	1.00 [0.07, 14.45]	2007
Meade 2008	53	475	47	508	78.2%	1.21 [0.83, 1.75]	2008
Huh 2009	3	30	3	27	4.7%	0.90 [0.20, 4.09]	2009
Xi 2010	0	55	0	55		Not estimable	2010
Hodgson 2011	0	10	0	10		Not estimable	2011
Liu 2011	2	50	4	50	4.0%	0.50 [0.10, 2.61]	2011
Kacmarek 2014	6	99	8	101	10.4%	0.77 [0.28, 2.13]	2014
Total (95% CI)		**749**		**779**	**100.0%**	**1.07 [0.77, 1.48]**	
Total events	65		65				

Heterogeneity: Tau² = 0.00; Chi² = 3.12, df = 5 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.70)





https://jamanetwork.com/journals/jama/fullarticle/2654894

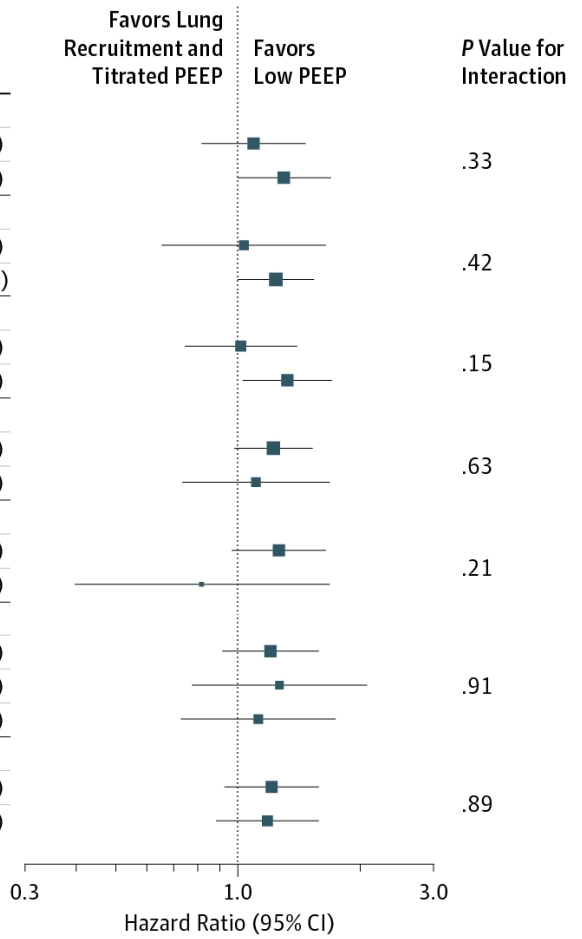


No. at risk								
Lung recruitment and titrated PEEP	501	397	340	303	276	254	233	225
Low PEEP	509	423	378	343	312	286	264	260

https://jamanetwork.com/journals/jama/fullarticle/2654894

At 28 days, 277 of 501 patients (55.3%) in the experimental group and 251 of 509 patients (49.3%) in the control group had died (HR: 1.20; 95%CI: 1.01 to 1.42; *P* = .041)

Subgroup	No. of Deaths/Total No. (%)		Hazard Ratio (95% CI)	*P* Value for Interaction
	Lung Recruitment and Titrated PEEP (n = 501)	Low PEEP (n = 509)		
PaO_2: FIO_2				
≤100 mm Hg	117/197 (59.4)	120/214 (56.1)	1.09 (0.82-1.46)	.33
>100 mm Hg	160/304 (52.6)	131/295 (44.4)	1.30 (1.00-1.69)	
Simplified Acute Physiology Score 3				
<50	47/117 (40.2)	48/119 (40.3)	1.03 (0.65-1.64)	.42
≥50	230/384 (59.9)	203/390 (52.1)	1.24 (1.00 -1.54)	
Type of ARDS				
Extrapulmonary	98/188 (52.1)	102/196 (52)	1.02 (0.74-1.40)	.15
Pulmonary	179/313 (57.2)	149/313 (47.6)	1.32 (1.03-1.69)	
Duration of ARDS at randomization, h				
≤36	214/388 (55.2)	196/405 (48.4)	1.22 (0.98-1.52)	.63
>36 to <72	63/113 (55.8)	55/104 (52.9)	1.11 (0.73-1.67)	
Position 1 h after randomization				
Supine (dorsal decubitus) or lateral decubitus	153/274 (55.8)	132/273 (48.4)	1.26 (0.96-1.64)	.21
Prone	19/31 (61.3)	20/30 (66.7)	0.82 (0.40-1.67)	
Duration of mechanical ventilation before randomization, d				
0-2	160/297 (53.9)	152/320 (47.5)	1.20 (0.92-1.56)	.91
3-4	54/88 (61.4)	41/77 (53.2)	1.26 (0.77-2.07)	
≥5	63/116 (54.3)	58/112 (51.8)	1.12 (0.73-1.71)	
Protocol modification				
Before	151/273 (55.3)	138/280 (49.3)	1.21 (0.93-1.57)	.89
After	126/228 (55.3)	113/229 (49.3)	1.18 (0.88-1.58)	



https://jamanetwork.com/journals/jama/fullarticle/2654894

Links de cursos:

- https://www.coursera.org/learn/revisao-sistematica
- https://www.coursera.org/learn/systematic-review

REFERENCIAS

1. Grady D & Hearst N. **Usando Bases de Dados Existentes**. Em: Hulley SB, Cummings SR, Browner WS, Grady DG & Newman TB. **Delineando a Pesquisa Clínica – Uma abordagem epidemiológica**. 3ª Ed. 2008. Cap. 13. **p. 231-240**.

2. Pabalan N, Jarjanazi H, Steiner T S. **Meta-analysis in microbiology**. Indian J Med Microbiol 2014;32:229-35

3. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). **Preferred Reporting Items for Systematic Reviews and MetaAnalyses: The PRISMA Statement**. PLoS Med 6(7): e1000097. doi:10.1371/ journal.pmed.1000097

4. Díaz-Quijano FA. **Predictores de sangrado espontáneo en dengue: una revisión sistemática de la literatura**. Invest. clín. 2008; 49(1): 111-122. Disponible en: http://ve.scielo.org/scielo.php?script=sci_arttext&pid=S0535-51332008000100012&lng=es.

5. Suzumura EA, Figueiró M, Normilio-Silva K, Laranjeira L, Oliveira C, Buehler AM, Bugano D, Passos Amato MB, Ribeiro Carvalho CR, Berwanger O, Cavalcanti AB. **Effects of alveolar recruitment maneuvers on clinical outcomes in patients with acute respiratory distress syndrome: a systematic review and meta-analysis.** Intensive Care Med. 2014 Sep;40(9):1227-40. doi: 10.1007/s00134-014-3413-6. Epub 2014 Aug 6. PMID: 25097070.

6. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators. **Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial.** *JAMA.* 2017;318(14):1335–1345. doi:10.1001/jama.2017.14171