Online data supplement

Diagnostic Yield and Safety of Transbronchial Lung Cryobiopsy and Surgical Lung Biopsy in Interstitial Lung Diseases – a systematic review and meta-analysis

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Supplementary Table 1 - Characteristics of the included studies

First Author (Year)	Country	Study Design	Biopsy method	Subjects, *N*	Age *	Male % (male/female)
Frutcher (2014)[41]	Israel	Retrospective cohort	TBLC	75	56.2 (± 16.0)	55 (41/34)
Griff (2014)[32]	Germany	Retrospective cohort	TBLC	52	63.0 (± 13.0)	69 (36/16)
Pajares (2014)[40]	Spain	Randomized clinical trial	TBLC	39	60.0 (± 10,3)	51 (20/19)
Hernández-González (2015)[42]	Spain	Retrospective cohort	TBLC	33	64.0 (30-79)	33 (11/22)
Cascante (2016)[45]	Spain	Prospective cohort	TBLC	55	58.8 (± 8.9)	58 (32/23)
Kronborg-White (2016)[43]	Denmark	Prospective cohort	TBLC	38	61.0 (29–80)**	58 (22/16)
Ramaswamy (2016)[44]	United States	Retrospective cohort	TBLC	56	60.0 (± 12.0)	54 (30/26)
Bango-Álvarez (2017)[22]	Spain	Prospective cohort	TBLC	106	60.0 (33-81)	65 (69/37)
Lentz (2017)[46]	United States	Retrospective cohort	TBLC	104	58.2 (20-83)	56 (58/46)
Linhas (2017)[24]	Portugal	Prospective cohort	TBLC	90	60.0 (± 13.0)	59 (53/37)
Cho (2018)[23]	United States	Retrospective cohort	TBLC	40	57.2 (± 13.0)	70 (28/12)
Cooley (2018)[25]	United States	Retrospective cohort	TBLC	159	57.0 (± 14.0)	46 (73/86)
Dhooria (2018)[26]	India	Retrospective cohort	TBLC	128	51.3 (± 13.9)	41 (53/75)
Abdelghani (2019)[27]	United States	Prospective cohort	TBLC	40	63.0 (26-82)	60 (24/16)
Çirak (2019)[30]	Turkey	Retrospective cohort	TBLC	82	58.4 (±9.33)	54 (44/38)
Hagmeyer (2019)[29]	Germany	Cross sectional	TBLC	61	66.0 (± 11.0)	59 (36/25)
Harari (2019)[28]	Italy	Retrospective cohort	TBLC	73	66.6 (± 8.6)	62 (45/28)
Hetzel (2019)[18]	Germany	Prospective cohort	TBLC	359	62.8 (± 14.0)	55 (198/153)
Samitas (2019)[15]	Canada	Retrospective cohort	TBLC	50	61.0 (43–81)**	58 (29/21)
Shafiek (2019)[31]	Egypt	Randomized clinical trial	TBLC	12	45.6 (± 9.2)	33 (4/8)
Aburto (2020)[37]	Spain	Prospective cohort	TBLC	257	63.3 (± 11.8)	65 (166/91)
Bondue (2020)[34]	Belgium	Prospective cohort	TBLC	81	62.0 (26–81)**	49 (40/41)
Gnass (2020)[38]	Poland	Prospective cohort	TBLC	114	54.0 (±14)	52 (59/55)
Hussein (2020)[39]	Egypt	Prospective cohort	TBLC	23	46.2 (± 13.5)	35 (8/15)
Koslow (2020)[33]	United States	Retrospective cohort	TBLC	120	62.0 (± 14.0)	56 (67/53)
Pajares (2020)[40]	Spain	Prospective cohort	TBLC	124	65.7 (± 11.9)	58 (72/52)
Wang (2020)[36]	China	Prospective cohort	TBLC	70	62.7 (± 8.4)	34 (24/46)
Ravaglia (2016)[59]	Italy	Retrospective	TBLC	297	60.0 (21–78)**	58 (172/125)

		cohort	VATS	150	59.0 (15-74)**	57 (85/65)
Romagnoli (2019)[61]	France, Italy	Cross sectional	TBLC	21	65.0 (60-69)**	48 (10/11)
			VATS	21		48 (10/11)
Troy (2019)[60]	Australia	Cross sectional	TBLC	65	66.1 (± 9.3)	48 (31/34)
			VATS	65	66.1 (± 9.3)	48 (31/34)
Fibla (2012)[2]	Spain	Prospective cohort	VATS	224	57.1 (25-77)	48 (106/118)
Kayatta (2013)[52]	United Kingdom	Retrospective cohort	VATS	194	58.0	52 (113/81)
Luo (2013)[51]	China	Retrospective cohort	VATS	32	52.2 (30-76)	63 (20/12)
Pompeo (2013)[47]	Italy	Prospective cohort	VATS	30	62.0 (± 10)	50 (15/15)
Morris (2014)[53]	United Kingdom	Retrospective cohort	VATS	66	58.9	47 (31/35)
Bagheri (2015)[54]	Iran	Retrospective cohort	VATS	38	47.7 (22-79)	50 (19/19)
Samejima (2015)[55]	Japan	Retrospective cohort	VATS	285	65.0 (18-85)**	57 (161/124)
Khalil (2016)[56]	United Kingdom	Retrospective cohort	VATS	115	NA	NA
Lieberman (2017)[57]	United States	Retrospective cohort	VATS OLB	45 2	57.4 (± 12.8)	44.7 (21/26)
Jeon (2018)[58]	South Korea	Retrospective cohort	VATS	35	NA	54 (19/16)
Sugino (2019)[48]	Japan	Retrospective cohort	VATS	143	64.0 (33-81)**	48 (69/74)
Cherchi (2020)[50]	Italy	Retrospective cohort	VATS	99	66.0 (± 10)	73 (74/26)
Pastre (2020)[49]	United States	Retrospective cohort	VATS	268	63.0 (± 13)	54 (144/124)

* Results are presented as mean (± standard deviation or range) unless stated otherwise
** Median (range)

Supplementary Table 2 - Summary of the characteristics of the included studies by type and region

		TBLC	VATS
Study design, n	Retrospective cohort	13 *	12 *
	Prospective cohort	12	2
	Cross sectional	3 **	2 **
	Randomized controlled trial	2***	0
	Total	30	16
Continent, n	Europe	16 †	7 †
	North America	7	3
	Asia	4	5
	Australia	1 ‡	1 ‡
	Africa	2	0
	Total	30	16

* One of the retrospective cohorts deals with TBLC and SLB.

** Two of the cross sectional studies deal with TBLC and SLB.

*** Two randomized controlled trial comparing TBLC with conventional forceps sampling.

† Two of the European cohorts deal with TBLC and SLB.

‡ The Australian cohort deals with TBLC and SLB.

Supplementary Table 3 - Biopsy method and characteristics of samples

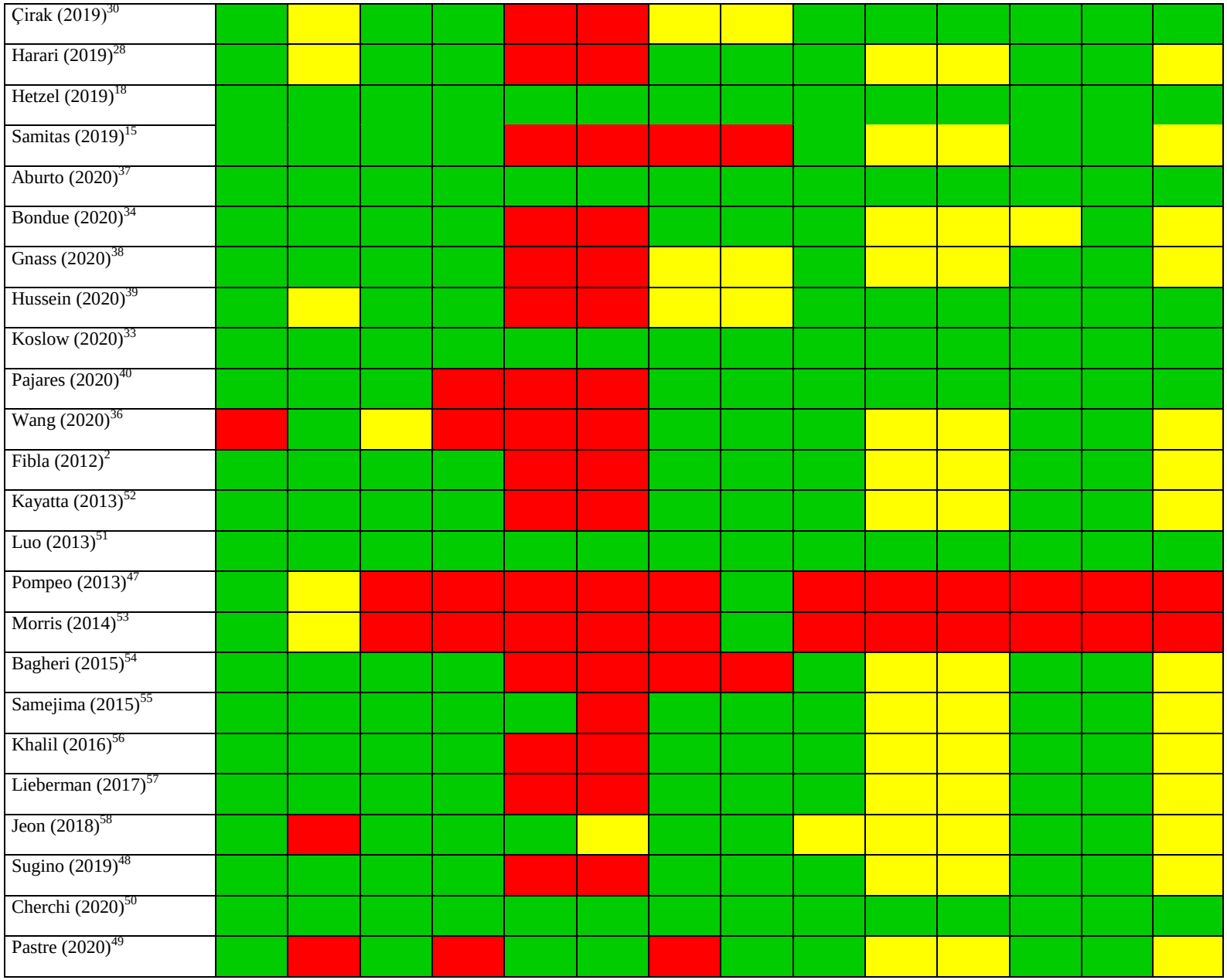
First Author (Year)	Biopsy method (n)	No. of Samples/Subject*	Surface Area of Samples, mm^2 *	Diameter, mm*	Cryoprobe Diameter (mm)	Cooling time (s)	UIP pattern, n (%)
Frutcher (2014)[41]	TBLC (75)	3 (2-4)	9 (6-18)	NA	2.4	4	7 (9.3)
Griff (2014)[32]	TBLC (52)	1-2	NA	6.9 (± 4.4)	1.9	3-5	11 (21.0)
Pajares (2014)[40]	TBLC (39)	3.7 (± 0.9)	14.7 (± 11)	4.1 (± 1.5)	2.4	3–4	7 (17.9)
Hernández-González (2015)[42]	TBLC (33)	2.7 (0–5)	NA	4 (± 1.7)	1.9	3–4	6 (18.2)
Cascante (2016)[45]	TBLC (55)	2.8 (1-5)	20.7 (2-42)	NA	2.4	3-4	18 (32.7)
Kronborg-White (2016)[43]	TBLC (38)	4**	NA	6.4 (± 2.5)	1.9 or 2.4	5 to 7	10 (26.3)
Ramaswamy (2016)[44]	TBLC (56)	2 (1-4)	NA	4 – 26	2.4	4–5	NA
Bango-Álvarez (2017)[22]	TBLC (106)	3	15.7 (± 9)	5.1	1.9	5	22 (20.8)
Lentz (2017)[46]	TBLC (104)	2.2 (± 0,6)	NA	6.9	1.9	4–5	19 (18.3)
Linhas (2017)[24]	TBLC (90)	NA	NA	NA	2.4	5	18 (20.0)
Cho (2018)[23]	TBLC (40)	5.17 (± 1.2)	40.0 (± 2)	5.7 (± 2)	1.9	4-12	1 (3.0)
Cooley (2018)[25]	TBLC (159)	4. 9 (± 1.47)	NA	6.1 (± 2.2)	1.9 or 2.4	6.1 (± 1.3)	11 (6.9)
Dhooria (2018)[26]	TBLC (128)	3 (1–7)**	NA	5 (2–10)**	1.9	5 (3–8)	11 (8.6)
Abdelghani (2019)[27]	TBLC (40)	3.45 (± 1.2)	36.2 (± 21.5)	NA	1.9	5-7	15 (37.5)
Çirak (2019)[30]	TBLC (82)	3	NA	2 – 3	2.4	3 to 6	21 (25.6)
Hagmeyer (2019)[29]	TBLC (61)	NA	NA	NA	1.9	3-4	18 (29.5)
Harari (2019)[28]	TBLC (73)	3-4	NA	5	1.9	3-6	39 (61.0)
Hetzel (2019)[18]	TBLC (359)	3.2 (± 1.2)	NA	NA	1.9 or 2.4	3 to 7	NA
Samitas (2019)[15]	TBLC (50)	2.75 (± 0.9)	NA	5.2 (±1. 83)	1.9	3–5	3 (6.0)
Shafiek (2019)[31]	TBLC (12)	2-4	NA	3.9 (± 1.2)	2.4	NA	NA
Aburto (2020)[37]	TBLC (257)	4 (1–5)**	NA	NA	2.4	4	NA
Bondue (2020)[34]	TBLC (81)	4 (1–5)	20.9 (9-44)	NA	1.9 or 2.4	NA	21 (26.0)
Gnass (2020)[38]	TBLC (114)	2-5	NA	7 (5-10)	1.9	5-8	8 (7.0)
Hussein (2020)[39]	TBLC (23)	2-3	NA	10.2 (± 1.4)	2.4	3 to 6	2 (8.7)
Koslow (2020)[33]	TBLC (120)	3-6	NA	NA	1.9	3-7	NA
Pajares (2020)[40]	TBLC (124)	3.5	NA	NA	2.4	3-4	10 (8.1)
Wang (2020)[36]	TBLC (70)	NA	NA	NA	2.4	NA	4 (5.7)

Ravaglia (2016)[59]	TBLC (297)	1-8	44.4	NA	2.4	5	92 (31)
	VATS (150)	NA	NA	NA	-	-	74 (49.3)
Romagnoli (2019)[61]	TBLC (21)	5 (2-6)**	NA	7 (5-8)**	2.4	5-6	9 (42.9)
	VATS (21)	2	NA	46.1 (±13.8)	-	-	8 (38.1)
Troy (2019)[60]	TBLC (65)	5 (3-7)**	NA	7.1 (± 1.9)	1.9 or 2.4	4.6 (± 0.7)	41 (63.0)
	VATS (65)	NA	NA	46.5 (± 14.9)	-	-	39 (60.0)
Fibla (2012)[2]	VATS (224)	1-2	NA	NA	-	-	NA
Kayatta (2013)[52]	VATS (196)	2-3	NA	NA	-	-	83 (42.0)
Luo (2013)[51]	VATS (32)	1-2	NA	NA	-	-	4 (12.5)
Pompeo (2013)[47]	VATS (30)	1.8 (± 0.4)	NA	NA	-	-	13 (43.3)
Morris (2014)[53]	VATS (66)	NA	NA	NA	-	-	19 (28.8)
Bagheri (2015)[54]	VATS (38)	NA	NA	NA	-	-	9 (23.7)
Samejima (2015)[55]	VATS (285)	2 (1-3)	NA	NA	-	-	NA
Khalil (2016)[56]	VATS (115)	1-3	NA	NA	-	-	31 (27.0)
Lieberman (2017)[57]	VATS (45) OLB (2)	NA	NA	NA	-	-	NA
Jeon (2018)[58]	VATS (35)	NA	NA	NA	-	-	12 (34.3)
Sugino (2019)[48]	VATS (143)	1-3	NA	NA	-	-	31 (21.7)
Cherchi (2020)[50]	VATS (99)	1.2 (± 0.4)	NA	NA	-	-	60 (61.0)
Pastre (2020)[49]	VATS (268)	NA	NA	NA	-	-	67 (25.0)

*Results are presented as mean (± standard deviation or range) or range unless stated otherwise
** Median (range)

Supplementary Table 4 - Quality Assessment of studies (CASP Cohort Study Checklist)

CASP Cohort Study Checklist														
First Author (Year)	Validity of the study								Results			Usefulness of results		
	Focused issue	Cohort recruited	Exposure measured	Outcome measured	Identification of the confounding factors	Consideration of the confounding factors	Follow up of subjects complete enough	Follow up of subjects long enough	Results	Precision of results	Believe in results	Application of the results in the local population	Fit with other available evidence	Implications of this study
Frutcher (2014)[41]														
Griff (2014)[32]														
Hernández-González (2015)[42]														
Cascante (2016)[45]														
Kronborg-White (2016)[43]														
Ramaswamy (2016)[44]														
Ravaglia (2016)[59]														
Bango-Álvarez (2017)[22]														
Lentz (2017)[46]														
Linhas (2017)[24]														
Cho (2018)[23]														
Cooley (2018)[25]														
Dhooria (2018)[26]														
Abdelghani (2019)[27]														


Çirak (2019)[30]
Harari (2019)[28]
Hetzel (2019)[18]
Samitas (2019)[15]
Aburto (2020)[37]
Bondue (2020)[34]
Gnass (2020)[38]
Hussein (2020)[39]
Koslow (2020)[33]
Pajares (2020)[40]
Wang (2020)[36]
Fibla (2012)[2]
Kayatta (2013)[52]
Luo (2013)[51]
Pompeo (2013)[47]
Morris (2014)[53]
Bagheri (2015)[54]
Samejima (2015)[55]
Khalil (2016)[56]
Lieberman (2017)[57]
Jeon (2018)[58]
Sugino (2019)[48]
Cherchi (2020)[50]
Pastre (2020)[49]

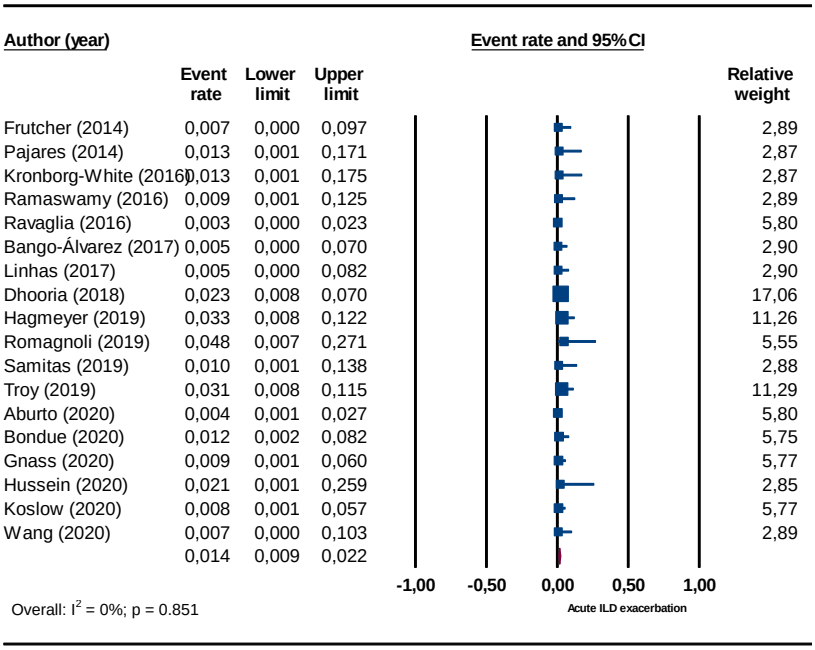
Supplementary Table 5 - Quality Assessment of studies (CASP Diagnostic Study Checklist)

CASP Diagnostic Study Checklist												
First Author (Year)	Validity of the study								Results			Usefulness of results
	Clear question	comparison with a reference	Patients get both tests	Reference influence	disease status	methods	results	Believe in results	Application of the results in the local population	Application of the test in the local population	All outcomes considered	Impact of the test
Hagmeyer (2019)[18]												
Romagnoli (2019)[61]												
Troy (2019)[60]												

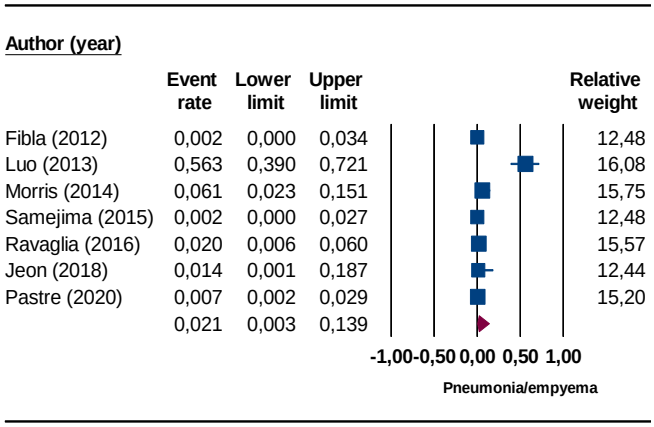
Supplementary Table 6 - Quality Assessment of studies (CASP Randomised Controlled Trial Checklist)

CASP Randomised Controlled Trial Checklist											
First Author (Year)	Validity of the study						Results		Usefulness of results		
	Focused issue	Randomization of treatments	Patients accounted for conclusion	Blind to treatment	Similarity of groups	Equality of treatments within groups	Treatment effect	Precision of the treatment effect	Application of the results in the local population	Consideration of the important outcomes	Analysis of benefits, harms, and costs
Pajares (2014)[40]											
Shafiek (2019)[31]											

Supplementary Figure 1 - Acute ILD exacerbation after TBLC. The diamond indicates the pooled effect.



*Supplementary Figure 2 - Complications after VATS: **a)** Pneumonia/empyema; **b)** thoracic pain; **c)** persistent air-leak; **d)** acute ILD exacerbation. The diamond indicates the pooled effect.*



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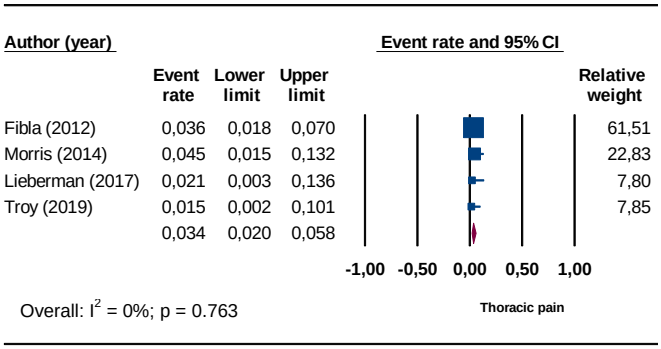

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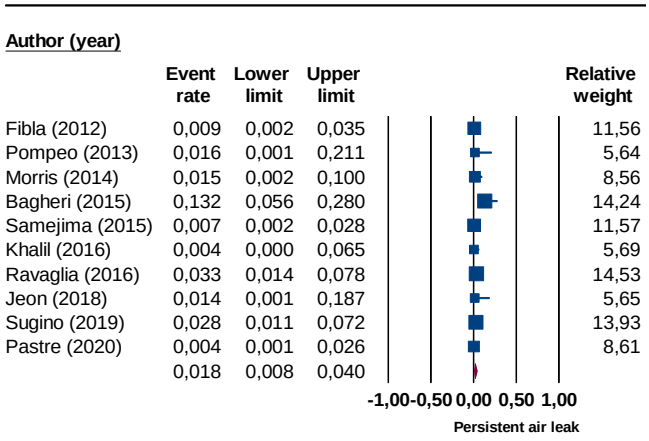

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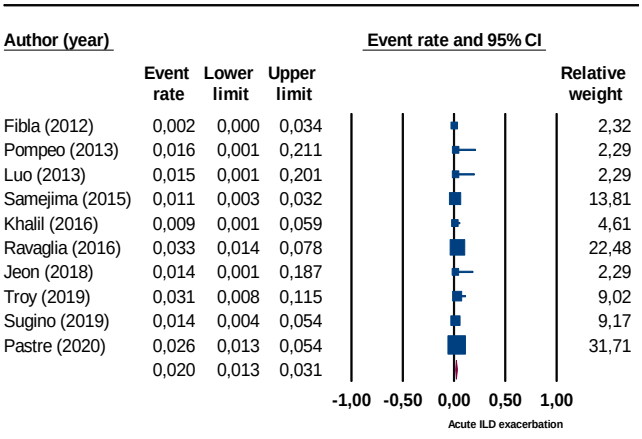

d)