Original Article Efficacy and safety between the anterior and posterior surgery in treating the ossification of posterior cervicallongitudinal ligament (OPLL): a meta-analysis

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Abstract: Background: The ossification of the posterior cervical longitudinal ligament (OPLL) is one of the main causes of cervical spondylitis myelopathy (CSM). Apart from conservative approaches, both anterior and posterior surgeries have been introduced into clinical practices for managing OPLL patients. Methods: Electronic databases including PubMed, Embase and CNKI were searched to retrieve eligible publication sir respective of language restrictions. Only studies compared the efficacy and safety between anterior and posterior surgery were included. All extracted data were expressed as standard mean difference (SMD) with 95% confidential interval (95% CI) in the forest plot. In addition, heterogeneity among studies was assessed through the l^2 and P-value as well. Finally, publication bias was evaluate dusing the comparison-adjusted funnel plot. Results: A total of 33 studies with 2,910 subjects were contained in this meta-analysis. The pooled SMD of post-operative JOA score was 0.70 with 95% CI from 0.39 to 1.00, suggesting significant difference between these two surgical strategies. The merged SMD of IR was 0.48 with 95% CI from 0.25 to 0.72, which confirmed the same results gained from JOA score. The pooled SMD for operation time was 0.84 with a 95% CI from 0.25 to 1.42. No publication bias was found for each outcome. Conclusions: The anterior approach had relatively better performance with respect to efficacy in managing OPLL or CSM. Since there was no significant difference in blood loss or complications between the anterior and posterior surgery, safety between these two approaches may be similar. As suggested by a shorter operation time, the posterior surgery seemed to be better than anterior surgery. Therefore, OPLL patients managed by the anterior surgery may benefit from its relatively strong effectiveness, while posterior surgery is comparatively safe for OPLL patients. More studies should be carried out to confirm the above conclusions.

Keywords: Ossification of the posterior cervical longitudinal ligament, cervical spondylotic myelopathy, anterior surgery, posterior surgery, Japanese orthopedic association score, improvement rate, meta-analysis

Introduction

The ossification of the posterior cervical longitudinal ligament (OPLL) is an abnormal calcification of the posterior longitudinal ligament which is located in the cervical spine. This disease not only forms the lesion of the spinal canal but also causes the sensory dysfunction, dyskinesia and the disorder of autonomic nervous system [1]. OPLL has been considered as a common cervical myelopathy and approximately a quarter of cervical myelopathy patients have experience OPLL [2]. The prevalence of OPLL in Asian was about 2.4% and this figure is much higher than that in other ethnicities [1]. As suggested by the Investigation Committee on OPLL of the Japanese Ministry of Public Health and Welfare, males are more likely to develop OPLL than females and the average on-set age of this disease is over 40 [3, 4]. Although genetic factors, medication of hormonal, environmental hazards and life styles have been linked with OPLL, discovering the exact pathogenesis of OPLL is still challenging. It is also challenging to diagnose OPLL since patients usually have no significant symptoms at early stages [1]. As a result, OPLL may progress gradually which may lead to severe neurological complications.

Plain radiographs, computed tomography scanning, conventional lateral radiographic tomography and magnetic resonance imaging are turned out to be reliable techniques in diagnosing OPLL [5]. Conservative approaches in which surgeries are not involved are appropriate for patients with mild symptoms or those with choroba organiczna and these approaches include continuous skull traction, neck collar fixation and the application of non-steroidal anti-inflammatory drugs and neurotrophic drugs [6, 7]. Nevertheless, abundant studies have confirmed the predominant efficacy of surgical approaches over conservative approaches.

The anterior and posterior surgery are two common approaches used to manage OPLL patients with severe symptoms since conservative treatments may not be effective for these patients. These two approaches are designed to decompress the spinal cord and enlarge the spinal canal [8]. The anterior surgery refers to anterior cervical discectomy fusion (ACDF) or anterior cervical corpectomy fusion (ACCF) whereas posterior surgeries include laminectomy, laminectomy combined with instrumented arthrodesis and laminoplasty [9]. Theoretically, the anterior surgery is considered as an optimal choice for resecting ossification sites of posterior longitudinal ligament which is located below the third or fourth cervical vertebrae [10]. Besides that, the posterior surgery is also applied in clinical practices and this approach enlarges the spinal canal through removing or trimming the lamina of vertebra [11].

Both the anterior and posterior surgery may be recommended for patients, but their efficacy and tolerance is still unclear. Although a large number of studies have compared the efficacy and safety of these two approaches, contradictory results have been revealed by the literature. For instance, a study conducted by Liu et al. suggested that the improvement rate (IR) for anterior surgery was 77.0% ± 21.3% whereas this figure for posterior surgery was 68.1% ± 22.8% [12]. Another study by Seng et al. concluded that posterior surgery exhibited more desirable performance than anterior surgery with respect to IR [13]. As a result of this, we designed ameta-analysis for addressing the inconsistency among current literatures. We compared the efficacy and safety of these two approaches by analyzing the pre-operation and post-operation JOA scores, IR, blood loss, operation time and risk of complications. This elegant approach is to provide clinicians with the corresponding guidance for selecting the appropriate surgery for OPLL patients.

Methods

Literature identification

Relevant literatures were identified through electronic searching from database of PubMed, Embase and Chinese National Knowledge Infrastructure (CNKI) without the limitation of languages. "Ossification of cervical posterior longitudinal ligament", "anterior surgery", "posterior surgery", "JOA score", "improvement rate" and their synonyms were used as searching terms. Additionally, all the reference lists of identified literatures were searched and examined manually in order to prevent the inappropriate omission of literatures. After that, all the potential literatures were retrieved by two reviewers and any disagreement was solved under discussion.

Inclusion criteria

The following inclusion criteria were specifically designed to determine the eligibility of studies: (i) subjects involved in the study must be diagnosed as OPLL or CSM irrespective of the cervical level; (ii) each patient must undergo one of the two surgeries (iii) at least one of the comparative outcomes of efficacy and safety suchas JOA score, IR value, blood loss, operation time or complications should be provided. The corresponding titles and abstracts of the retrieved literatures were screened by two reviewers independently, and if necessary, full text was examined for more details so that the final list of eligible studies can be formed. Studies that do not comply with the above inclusion criteria were not eligible for the analysis.

Data extraction and outcome measures

The following data were extracted from selective studies based on the inclusion criteria: author, the year of publication, country and researched disease; the information of patients including the average age, detailed surgical techniques, sample size, follow-up time and the involvement of segment; the outcome of each group including pre-operation and post-operation JOA scores, IR value, blood loss, operation



time and complication. JOA scores and IR values were considered as primary outcomes for assessing the effectiveness and safety of these two approaches. JOA scores with a maximum of 17 reflects the degree of dysfunction in CSM patients and it assesses the motor function, sensory function as well as the bladder function [14]. On the other hand, IR evaluates the neurological status of patients and it is calculated as: IR = (post-operative JOA score-preoperative JOA score)/(17-preoperative JOA score) × 100% [15]. Surgery outcomes were classified as excellent if IR exceeded 75%, as good if IR was between 50% and 75%, as fair if IR was between 25% and 50% and as poor when IR was lower than 25% [16].

Besides, the volume of blood loss, operation time and the number of complications were taken into account as secondary outcomes. Surgeries are considered as ineffective if it involves a large amount of blood loss or unexpectedly long operation time [17]. In addition, the number of complications was selected to evaluate the safety of surgeries. Common complications associated with surgeries include cerebrospinal fluid leakage, postoperative neck pain and postoperative C-5 nerve root palsy [18].

Statistical analysis

We carried out a meta-analysis to synthesize evidence from individual studies. Direct comparison between two surgeries was conducted by calculating the standard mean difference (SMD) of JOA score, IR value, blood loss and operation time. We also obtained 95% confidence intervals (95% CI) for these estimates as well as the weights of each study that are required for the meta-analysis. The corresponding SMD and odds ratios together with their 95% CIs were displayed using forest plots.

Additionally, heterogeneity among selected studies was evaluated through Cochran's *Q* and Higgins' *I*² statistic. The

percentage of variation across studies contributed by heterogeneity instead of chance was described by I², and it can be calculated by the formula: $l^2 = 100\% \times (Q-df)/Q$, where Q is Cochran's heterogeneity statistic and df represents the degrees of freedom (the number of studies) [19]. Significant heterogeneity was presented if $P_{h} < 0.05$ or $I^{2n} > 50\%$ and a random effects model will be selected in such circumstances. Furthermore, the statistic tau² was estimated using the approach of restricted maximum likelihood estimation (RMLE) in order to appraise heterogeneity among included studies [20]. Finally, publication bias contributed by small study effects was assessed using the comparison-adjusted funnel plot in which SMD was plotted as the horizontal axis whereas standard errors were plotted as the vertical axis.

Results

Included studies

As suggested by the literature flow diagram **Figure 1**, a total of 683 studies had been identified through both electronic and manual searching in which 47 articles among them were excluded for duplicates. The correspond-

 Table 1. The main characteristics of included studies

Author	Year	Country	Lan- guage	Randomization	Dis- ease	Age	Surgical approach	No.	Follow-up (month)	Involvement (segments)	Outcomes
Chen	2008	China	Chinese	No (Retrospective)	OPLL	57.2	A: ACCF	14	18	1-3	1236
							P: Laminoplasty	20		≥3	
Liu	2010	China	Chinese	No (Retrospective)	OPLL	58.0	A: ACCF	29	31	≤3	12
						54.0	P: Laminoplasty	25	35	≤3	
Zhang	2012	China	Chinese	No (Retrospective)	OPLL	58.3	A: ACCF	20	12	2.2	126
							P: Laminoplasty	28		4.5	
Wu	2009	China	Chinese	No (Retrospective)	OPLL	54.6	A: ACCF	46	33.6	-	123
							P: Laminoplasty	59		-	
Chen	2010	China	Chinese	No (Retrospective)	OPLL	55.3	A: ACCF	51	12	≤3	6
							P: Laminoplasty	75		≥ 3	
Wang	2008	China	Chinese	No (Prospective)	OPLL	62.2	A: ACCF	16	12-24	≤ 3	12346
							P: Laminoplasty	6		≥ 3	
Yu	2013	China	English	No (Retrospective)	CSM	59.6	A: ACCF	29	12-42	4	123456
							P: Laminectomy	24		4	
Shibuya	2010	Japan	English	No (Retrospective)	CSM	60.4 ± 8.4	A: ACCF	34	12.1	1-4	345
						64.8 ± 11.7	P: Laminoplasty	49	17.6	2-4	
Seng	2013	Singapore	English	No (Retrospective)	CSM	58.7 ± 10.7	A: ACCF or ACDF	56	6	1-2	12345
						60.7 ± 10.8	P: Laminoplasty	42	6	3-4	
Sah	2012	Nepal	English	No (Prospective)	CSM	56.0 ± 12.0	A: ACCF and ACDF	20	3	-	1234
						52.0 ± 8.0	P: Laminoplasty	20	3	-	
Liu	2012	China	English	No (Retrospective)	CSM	53.9 ± 10.7	A: ACCF	71	31.2	≥2	123
						57.1 ± 10.4	P: Laminectomy	45	31.2	≥2	
Lin	2013	China	English	Unclear	CSM	52.2 ± 9.7	A: ACCF and ACDF	27	39.8 ± 5.2	4	12345
						54.5 ± 10.3	P: Laminectomy	24	41.5 ± 6.4	4	
Lin	2012	China	English	No (Retrospective)	OPLL	54.7 ± 13.2	A: ACCF	26	36.3 ± 6.4	3-4	12345
						56.2 ± 14.1	P: Laminectomy	30	37.6 ± 6.7	3-4	
Kristof	2009	Sweden	English	No (Retrospective)	CSM	62.5 ± 10.6	A: ACCF	42	196.56 ± 212	2	45
						66.0 ± 12.4	P: Laminectomy	61	66.53 ± 34.21	2	
Jain	2005	India	English	No (Retrospective)	OPLL	51.5 ± 8.4	A: ACCF	14	20 ± 19	3-4	3
						56.1 ± 10.8	P: Laminectomy	13	16.3 ± 10.9	3-4	
Hirai	2011	Japan	English	No (Prospective)	CSM	59.2 ± 10.7	A: Decompression and fusion	39	60	2	12345
						61.2 ± 10.1	P: Laminoplasty	47		3-4	
Ghogawala	2011	USA	English	Yes	CSM	60.0	A: ACCF	28	12	-	12
						64.0	P: Laminectomy	22	12	-	
Huo	2010	China	Chinese	No (Retrospective)	OPLL	55.9 ± 11.7	A: Decompression and fusion	11	12	1.9 ± 0.7	123456
						54.9 ± 9.0	P: Laminoplasty	14	12	2.4 ± 0.4	

Comparison of anterior and posterior surgeries for treating OPLL

Fehlings	2013	USA	English	No (Prospective)	CSM	52.5 ± 10.6	A: ACCF and ACDF	169	12	-	12
						62.8 ± 10.7	P: Laminectomy and Laminoplasty	95	12	-	
Cabraja	2010	Germany	English	Unclear	CSM	60.4 ± 9.9	A: ACCF	39	33	1-2	(126)
						66.2 ± 8.8	P: Laminectomy	28	33	2-4	
Edwards	2002	USA	English	No (Retrospective)	CSM	53.0 ± 8.3	A: ACCF	13	49	≥2	6
						54.0 ± 8.0	P: Laminectomy	25	40	≥2	
Chen	2011	China	English	No (Retrospective)	OPLL	57.2	A: ACCF	22	48	3.3 ± 0.3	1236
						55.3	P: Laminectomy and Laminoplasty	53		3.59 ± 0.22	
Li	2015	China	English	No (Retrospective)	CSM	53.9 ± 9.6	A: ACCF and ACDF	19	18.0 ± 6.6	≥3	123456
						56.3 ± 9.7	P: Laminoplasty	76	20.3 ± 8.0	≥3	
Lau	2015	USA	English	No (Retrospective)	CSM	54.8 ± 12.9	A: ACCF	20	32.1 ± 25.2	3	46
						54.9 ± 9.6	P: ACDF	35	22.1 ± 17.7	3	
Kim	2015	Korea	English	No (Retrospective)	OPLL	57.3 ± 10.3	A: Decompression and fusion	71	48 ± 14	-	12
						56.4 ± 10.3	P: Laminoplasty	64	41 ± 9.5	-	
Wang	2006	China	English	No (Retrospective)	CSM	54.8	A: Decompression and fusion	27	42.6	2-3	123
							P: Laminoplasty	15	42.6	3-4	
Wada	2001	Japan	English	No (Retrospective)	CSM	52.7 ± 7.8	A: ACCF	23	15.0 ± 2.7	2-4	1245
						56.5 ± 11.2	P: Laminoplasty	24	11.7 ± 0.9	2-4	
Sakai	2012	Japan	English	No (Prospective)	OPLL	59.5 ± 9.3	A: Decompression and fusion	20	60	≥2	123456
						58.4 ± 9.6	P: Laminoplasty	22		≥2	
Masaki	2007	Japan	English	No	OPLL	51.8 ± 6.6	A: Decompression and Fusion	19	12	2.9 ± 0.9	123
						62.6 ± 10.3	P: Laminoplasty	40	12	4.6 ± 0.5	
Liu	2011	China	English	No	CSM	54.6 ± 11.5	A: ACDF	25	25.40 ± 13.76	1-3	123456
						57.3 ± 10.1	P: Laminoplasty	27	27.47 ± 11.06	3-4	
Fang	2013	China	English	No (Prospective)	CSM	56.8 ± 11.7	A: ACDF	54	36	-	345
						58.2 ± 12.9	P: Laminoplasty	56		-	
Fujimori	2013	Japan	English	No (Retrospective)	OPLL	55.6 ± 7.8	A: ACDF	12	9.9 ± 4.1 (y)	2-4	12345
						58.7 ± 9.1	P: Laminoplasty	15	10.2 ± 5.7 (y)	2-4	
Iwasaki	2007	Japan	English	No (Retrospective)	OPLL	58.0 ± 8.3	A: Decompression and Fusion	27	6 ± 2 (y)	3	45
						57.0 ± 8.5	P: Laminoplasty	66	10.2 ± 3.75 (y)	3	

*OPLL: ossification of the posterior longitudinal ligament; CSM: cervical spondylotic myelopathy; A: anterior approaches; P: posterior approaches; ACDF: anterior cervical discectomy with fusion: ACCF: anterior cervical corpectomy with fusion; No.: number; y: year; ① JOA score-before operation; ② JOA score-post operation; ③ improvement rate; ④ blood loss; ⑤ operation time; ⑥ complications.

		Ante	rior										
Study	SD	Mean	n Tota	I SD	Mean	Total					SMD	95%CI	Weight
Chen 2008	1.80	9.30	14	1.60	8.70	20				-	0.35	[-0.34; 1.04]	3.5%
Liu 2010	4.21	9.11	29	4.38	9.35	25			+		-0.06	[-0.59; 0.48]	4.1%
Zhang 2012	1.60	9.20	20	1.70	9.00	28			+		0.12	[-0.46; 0.69]	3.9%
Wu 2009	2.08	9.49	46	1.88	9.67	59			+		-0.09	[-0.48; 0.30]	4.7%
Wang 2008	1.26	8.50	16	1.54	7.11	6				-	1.00	[0.01; 1.99]	2.5%
Yu 2013	1.93	7.28	29	1.77	7.21	24			+		0.04	[-0.50; 0.58]	4.1%
Seng 2013	3.00	11.00	56	3.00	11.00	42			+		0.00	[-0.40; 0.40]	4.6%
Sah 2012	1.03	8.30	20	1.23	7.60	20				-	0.60	[-0.03; 1.24]	3.7%
Liu 2012	2.50	9.50	71	2.70	10.50	45			-		-0.39	[-0.76; -0.01]	4.7%
Lin 2013	1.40	9.60	27	1.20	9.40	24			+		0.15	[-0.40; 0.70]	4.0%
Lin 2012	1.20	9.30	26	1.10	9.10	30			-		0.17	[-0.35; 0.70]	4.1%
Hirai 2011	3.10	9.90	39	2.90	9.70	47			+		0.07	[-0.36; 0.49]	4.5%
Ghogawala 2011	0.44	11.60	28	0.50	13.40	22 •	-				-3.79	[-4.75; -2.84]	2.6%
Huo 2010	2.00	8.50	11	2.80	8.70	14			-		-0.08	[-0.87; 0.71]	3.1%
Fehlings 2013	2.46	13.47	169	2.86	11.84	95			-	•	0.62	[0.37; 0.88]	5.1%
Cabraja 2010	2.10	12.50	39	3.20	11.70	28			- 🕈	•	0.30	[-0.19; 0.79]	4.3%
Chen 2011	1.80	9.30	22	1.25	8.61	53			-	-	0.48	[-0.03; 0.98]	4.2%
Li 2015	1.86	12.95	19	2.30	11.73	76			-	-	0.54	[0.04; 1.05]	4.2%
Kim 2015	4.00	12.00	71	3.00	12.00	64			+		0.00	[-0.34; 0.34]	4.9%
Wang 2006	2.80	8.80	27	2.60	9.40	15			-		-0.22	[-0.85; 0.42]	3.7%
Wada 2001	1.80	7.90	23	2.20	7.40	24			+	•	0.24	[-0.33; 0.82]	3.9%
Sakai 2002	2.80	11.40	20	2.30	10.90	22			-	•	0.19	[-0.41; 0.80]	3.8%
Masaki 2007	2.90	8.30	19	2.40	8.60	40			+		-0.12	[-0.66; 0.43]	4.1%
Liu 2012	3.41	8.59	25	2.98	8.16	27			+		0.13	[-0.41; 0.68]	4.1%
Fujimori 2013	2.20	9.50	12	2.60	9.10	15			+	•	0.16	[-0.60; 0.92]	3.2%
Random effects Heterogeneity:	Random effects model 878 865 0.06 [-0.15; 0.27] 100% Heterogeneity: <i>I</i> ² =76.4%, <i>tau</i> ² =0.2085, <i>P</i> <0.0001] 100%
									-	_	_		
Figure 2. The fo	rest plo	t of JOA	A score	be-			_4	-2	0	2	4		
fore the operation	fore the operation. Favours [posterior] Favours [anterior]												

	An	iteri	ior	Pos	steri	or					
Study	Mean	SD	Total	Mean	SD	Total			SMD	95%CI	Weight
Chen 2008	14 20	1 30	14	11.40	1 20	20		ί_	2 20	[132:308]	3.4%
Liu 2010	48 70	7 75	29	43.90	8.97	25		_	0.57	[1.02, 0.00]	4 1%
Zhang 2012	14 50	1 20	20	11 50	1 00	28		τ	2 71	[1.91: 3.52]	3.5%
Wu 2009	14.54	1.86	46	13.47	1.79	59		-	0.58	[0.19: 0.98]	4.4%
Wang 2008	14.75	0.93	16	13.33	1.73	6		<u> </u>	- 1.16	[0.14; 2.17]	3.1%
Yu 2013	13.17	1.65	29	13.13	1.45	24		ц.	0.03	[-0.52; 0.57]	4.1%
Seng 2013	12.40	1.70	56	13.70	3.10	42	-	1	-0.54	[-0.94; -0.13]	4.3%
Sah 2012	13.55	1.15	20	13.30	1.30	20	-	<u> </u>	0.20	[-0.42; 0.82]	3.9%
Liu 2012	11.30	1.80	71	10.70	2.00	45		-	0.32	[-0.06; 0.69]	4.4%
Lin 2013	13.90	1.30	27	13.10	1.50	24		-	0.56	[0.00; 1.13]	4.1%
Lin 2012	14.20	1.60	26	13.70	1.50	30	-		0.32	[-0.21; 0.85]	4.1%
Hirai 2011	14.90	2.30	39	13.10	2.90	47		+	0.67	[0.24; 1.11]	4.3%
Ghogawala 2011	15.44	0.99	28	13.54	0.45	22		• •	2.34	[1.60; 3.07]	3.7%
Huo 2010	14.60	1.90	11	12.60	3.00	14		÷.	0.75	[-0.07; 1.57]	3.5%
Fehlings 2013	15.94	0.23	169	15.46	0.34	95		1 -	1.74	[1.45; 2.04]	4.5%
Cabraja 2010	15.80	2.80	39	14.90	3.20	28			0.30	[-0.19; 0.79]	4.2%
Chen 2011	14.20	1.30	22	11.69	1.18	53		1 -	2 .04	[1.44; 2.64]	4.0%
Li 2015	15.34	1.40	19	14.92	1.56	76	-		0.27	[-0.23; 0.78]	4.2%
Kim 2015	15.60	4.25	71	15.00	4.00	64	- 1	⊷ ί	0.14	[-0.19; 0.48]	4.5%
Wang 2006	13.90	2.40	27	13.70	2.30	15		-	0.08	[-0.55; 0.71]	3.9%
Wada 2001	13.40	2.80	23	12.20	3.00	24	-	-	0.41	[-0.17; 0.98]	4.0%
Sakai 2002	15.10	2.20	20	14.00	2.60	22		-	0.45	[-0.17; 1.06]	4.0%
Masaki 2007	14.20	2.30	19	13.00	2.60	40		-	0.47	[-0.08; 1.03]	4.1%
Liu 2012	13.20	2.73	25	13.67	2.70	27	-	-í	-0.17	[-0.72; 0.37]	4.1%
Fujimori 2013	13.30	1.90	12	11.70	2.70	15	1	1	0.65	[-0.13; 1.43]	3.6%
Random effects n	nodel		878			865		?	0.70	[0.39; 1.00]	100%
Heterogeneity: /2=	=88.2%, ta	au²=0	. 5158 , P	<0.0001				í.			
Figure 3 The form	est nlot c	of IO		nost		-3 -2	2 -1 () 1	2 3		
operation.		1 50/	1 30016-	Fa	vour	s lposte	rior1	Fav	ours lanteri	orl	
Lin 2012 Hirai 2011 Ghogawala 2011 Huo 2010 Fehlings 2013 Cabraja 2010 Chen 2011 Li 2015 Kim 2015 Wang 2006 Wada 2001 Sakai 2002 Masaki 2007 Liu 2012 Fujimori 2013 Random effects m Heterogeneity: <i>I</i> ² = Figure 3. The fore operation.	14.20 14.90 15.44 14.60 15.94 15.80 14.20 15.34 15.60 13.90 13.40 15.10 14.20 13.20 13.30 model =88.2%, taget for the set of the s	1.60 2.30 0.99 1.90 0.23 2.80 1.30 1.40 4.25 2.40 2.20 2.20 2.20 2.23 1.90 u^2 =0	26 39 28 11 169 39 22 19 71 27 23 20 19 25 12 878 .5158 , P ⁴ A score-	13.70 13.10 13.54 12.60 15.46 14.90 11.69 14.92 15.00 13.70 12.20 14.00 13.00 13.67 11.70 <0.0001 post Fa	1.50 2.90 0.45 3.00 0.34 3.20 1.18 1.56 4.00 2.30 3.00 2.60 2.60 2.70 2.70	30 47 22 14 95 28 53 76 64 15 24 22 40 27 15 865 • -3 -2 's [poste	-1 (rior]		0.32 0.67 2.34 0.75 1.74 0.30 2.04 0.27 0.14 0.08 0.41 0.45 0.47 -0.17 0.65 0.70 2 3 ours [anterio	[-0.21; 0.85] [0.24; 1.11] [1.60; 3.07] [-0.07; 1.57] [1.45; 2.04] [-0.19; 0.79] [1.44; 2.64] [-0.23; 0.78] [-0.19; 0.48] [-0.55; 0.71] [-0.17; 0.98] [-0.17; 1.06] [-0.08; 1.03] [-0.72; 0.37] [-0.13; 1.43] [0.39; 1.00]	4.1% 4.3% 3.7% 4.5% 4.2% 4.2% 4.2% 4.2% 4.2% 4.5% 3.9% 4.0% 4.1% 3.6%

ing titles and abstracts of the remaining 636 articles were skimmed by two reviewers inde-

pendently. Except for the 542 irrelevant studies, full-text of 94 articles were reviewed and

Study Mean SD Total Mean SE Chen 2008 62.30 15.20 14 33.50 12.7 Wu 2009 74.95 9.83 46 69.90 9.5 Wang 2008 73.61 9.91 16 63.04 13.7 Yu 2013 59.86 17.63 29 60.18 12.0 Shibuya 2010 55.50 25.30 34 61.40 21.2	D Total 0 20 6 59 2 6 1 24 0 49 0 42 5 20 0 45	SMD 2.04 0.52 0.93 -0.02 -0.25 -0.12 -0.12	95%Cl [1.19; 2.90] [0.13; 0.91] [-0.06; 1.91] [-0.56; 0.52] [-0.69; 0.18] [-0.52; 0.28]	3.6% 5.7% 3.1% 5.0% 5.5%
Chen 2008 62.30 15.20 14 33.50 12.7 Wu 2009 74.95 9.83 46 69.90 9.5 Wang 2008 73.61 9.91 16 63.04 13.7 Yu 2013 59.86 17.63 29 60.18 12.0 Shibuya 2010 55.50 25.30 34 61.40 21.2	0 20 6 59 2 6 11 24 0 49 0 42 5 20 45	2.04 0.52 0.93 -0.02 -0.25 -0.12	[1.19; 2.90] [0.13; 0.91] [-0.06; 1.91] [-0.56; 0.52] [-0.69; 0.18] [-0.52: 0.28]	3.6% 5.7% 3.1% 5.0% 5.5%
Chen 2008 62.30 15.20 14 33.50 12.7 Wu 2009 74.95 9.83 46 69.90 9.5 Wang 2008 73.61 9.91 16 63.04 13.7 Yu 2013 59.86 17.63 29 60.18 12.0 Shibuya 2010 55.50 25.30 34 61.40 21.2	0 20 16 59 12 6 11 24 10 49 10 42 10 42 10 45	2.04 0.52 0.93 -0.02 -0.25 -0.12	[1.19; 2.90] [0.13; 0.91] [-0.06; 1.91] [-0.56; 0.52] [-0.69; 0.18] [-0.52] 0.28]	3.6% 5.7% 3.1% 5.0% 5.5%
Wu 2009 74.95 9.83 46 69.90 9.55 Wang 2008 73.61 9.91 16 63.04 13.7 Yu 2013 59.86 17.63 29 60.18 12.0 Shibuya 2010 55.50 25.30 34 61.40 21.2	6 59 2 6 11 24 00 49 00 42 00 42 00 45	0.52 0.93 -0.02 -0.25 -0.12	[0.13; 0.91] [-0.06; 1.91] [-0.56; 0.52] [-0.69; 0.18] [-0.52: 0.28]	5.7% 3.1% 5.0% 5.5%
Wang 2008 73.61 9.91 16 63.04 13.7 Yu 2013 59.86 17.63 29 60.18 12.0 Shibuya 2010 55.50 25.30 34 61.40 21.2	2 6 11 24 - 10 49 - 15 20 -	0.93 -0.02 -0.25 -0.12 -0.12	[-0.06; 1.91] [-0.56; 0.52] [-0.69; 0.18] [-0.52: 0.28]	3.1% 5.0% 5.5%
Yu 2013 59.86 17.63 29 60.18 12.0 Shibuya 2010 55.50 25.30 34 61.40 21.2	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	-0.02 -0.25 -0.12	[-0.56; 0.52] [-0.69; 0.18] [-0.52; 0.28]	5.0% 5.5%
Shibuya 2010 55.50 25.30 34 61.40 21.2	0 49 - 0 42 - 5 20 -	-0.25 -0.12	[-0.69; 0.18] [-0.52: 0.28]	5.5%
	0 42 -	-0.12	[-0.52: 0.28]	
Seng 2013 31.80 42.80 56 37.70 58.5	5 20 -	0.04		5.6%
Sah 2012 60.67 10.60 20 61.08 11.2	0 45	-0.04	[-0.66; 0.58]	4.6%
Liu 2012 77.00 21.30 71 68.10 22.8	45	0.40	[0.03; 0.78]	5.8%
Lin 2013 57.70 10.40 27 49.30 11.2	0 24	0.77	[0.20; 1.34]	4.8%
Lin 2012 58.60 10.40 26 54.80 9.7	0 30	0.37	[-0.16; 0.90]	5.0%
Jain 2005 63.27 20.21 14 58.85 15.3	8 13 🗕	0.24	[-0.52; 1.00]	4.0%
Hirai 2011 72.90 28.30 39 50.20 26.6	0 47	0.82	[0.38; 1.26]	5.4%
Huo 2010 74.40 18.40 11 45.30 24.1	0 14	1.29	[0.41; 2.17]	3.5%
Chen 2011 63.20 15.20 22 34.82 14.2	5 53	• 1.93	[1.34; 2.52]	4.7%
Li 2015 59.70 25.30 19 54.60 44.9	0 76 -	0.12	[-0.38; 0.62]	5.2%
Wang 2006 60.80 20.70 27 57.10 16.4	0 15 -	0.19	[-0.44; 0.82]	4.5%
Sakai 2002 71.40 26.00 20 55.30 29.6	0 22	0.57	[-0.05; 1.18]	4.6%
Masaki 2007 68.40 27.30 19 52.50 30.0	0 40	0.54	[-0.02; 1.09]	4.9%
Liu 2012 59.79 23.43 25 59.54 29.3	7 27 -		[-0.53; 0.55]	5.0%
Fang 2013 72.00 16.40 54 70.90 15.3	0 56 •	0.07	[-0.31; 0.44]	5.8%
Fujimori 2013 52.50 18.50 12 30.10 30.5	0 15	0.84	[0.04; 1.63]	3.8%
Random effects model 601 Heterogeneity: <i>I</i> ² =74.4%, <i>tau</i> ² =0.2134, <i>P</i> <0.0001	697	0.48	[0.25; 0.72]	100%
Figure 4. The forest plot of improvement rate.	-2 -1 rs [posterior]	0 1 2 Favours [anterio	or]	

	Α	nterio	r	Po	steric	or					
Study	Mear	ו SD ו	Tota	l Meai	n SD 1	Fotal			SMD	95%CI	Weight
Mana 2008	280.00	27.50	16	200.00	50.00	6			0.05	[2 50: 1 14]	4 70/
Wang 2006	260.00	37.50	10	300.00	140.46	24			-2.33	[-3.30, -1.14]	4.7%
10 2013 Shihuwa 2010	200.19	1215 55	29	403.41	140.40	24	_		-1.00	[-2.44, -1.15]	5.0%
Shibuya 2010	101.00	E4 00	54	404.00	420.00	49			1.13	[0.00, 1.00]	5.0%
Selly 2013	65.00	15.00	20	165.00	50.00	42	_		-0.01	[-1.22, -0.39]	5.9%
Jin 2012	250.00	121.00	20	284.00	120.00	20	· · · ·		-2.20	[-3.07, -1.45]	5.3%
Lin 2013	259.00	131.00	21	204.00	04.00	24		_	-0.20	[-0.75, 0.50]	5.7%
LIII 2012	703.00	749.00	20	310.00	94.00	30			2.20	[1.56, 2.94]	5.5%
Linai 2011	743.33	297.00	42	100 00	070.00	47			-0.12	[-0.51, 0.20]	5.9%
	540.00	207.00	39	222.40	92.10	47]		0.74	[0.30, 1.10]	5.0%
	310.20	420.00	10	332.10	140.90	14			0.00	[-0.21, 1.41]	5.5%
LI 2015	240.40	207.90	19	275.30	140.70	70		_	-0.17	[-0.07, 0.33]	5.0%
Lau 2015	362.20	245.10	20	117.90	09.00	35			1.00	[1.02, 2.30]	5.0%
Wada 2001	986.00	102.00	23	008.00	212.00	24			0.08	[0.09; 1.27]	5.7%
Sakal 2002	292.80	192.80	20	289.60	215.80	22			0.02	[-0.59; 0.62]	5.0%
LIU 2012	118.48	27.62	25	301.11	57.80	27			-5.21	[-6.39; -4.04]	4.7%
Fang 2013	192.00	47.00	54	175.00	39.00	50			0.39		5.9%
Fujimori 2013	600.00	459.00	12	240.00	153.00	15			1.07	[0.25; 1.89]	5.3%
Iwasaki 2007	513.00	415.00	27	464.00	437.50	66			0.11	[-0.34; 0.56]	5.8%
Random effects	model		500			638	•		-0.17	[-0.71; 0.37	7] 100%
Heterogeneity: I	²=94%, ta	u²=1.249), P<0.	.0001			1				
Figure 5. The for	est plot o	f the blo	od los	ss.		-6 -4	4 -2 (2	4 6		
					Favou	rs [poste	erior]	Favo	urs [ante	rior]	

61 of them did not provide adequate data for analysis. Finally, 33 studies with 2,910 subjects were included in the meta-analysis based on the inclusion criteria [9, 12, 13, 16, 21-49] (Table S1).

Characteristics of included studies

The main characteristics of eligible studies were illustrated in **Table 1** which included the

first author, the year of publication, country, disease, average age, detailed surgical approach, subjects, follow-up period in months, the corresponding segments and the corresponding outcomes. Studies that are related to CSM were also included in our analysis in order to enhance the statistical power of the analysis. The detailed operative techniques with respect to the anterior surgery included ACCF, ACDF, decompression and fusion. Laminoplasty and laminectomy are two specific approaches that are used for the posterior surgery.

JOA score

As suggested by Figures 2 and 3, 25 out of 33 included articles provided us with data for both pre-operative and post-operative JOA scores. The corresponding sample sizes for the anterior and posterior surgery group were 878 and 865, respectively. Significant differences in pre-operative JOA scores between the two approaches were suggested by five studies, whereas such differences appeared to be nonsignificant for the remaining studies. The corresponding SMDs of the two studies conducted by Wang et al. [50] and Ghogawala et al. [27] were 1.00 (95% CI from 0.01 to 1.99) and -3.79 (95% CI from -4.75 to 2.84). The randomeffects model was selected for analysis since the statistic of l^2 was 76.4% (> 50%). Since the pooled SMD of pre-operative JOA scores was 0.06 (95% CI from -0.15 to 0.27), no significant difference in pre-operative JOA scores was found between the anterior and posterior surgery. On the other hand, significant differences in post-operative JOA scores were suggested by 11 studies in which only one study favored the posterior approach [13] with SMD -0.54 (95% CI from -0.94 to -0.13). Significant heterogeneity also existed with respect to post-operative JOA scores since *l*² was 88.2%, and *P* value was less than 0.0001. The random-effects model concluded that the pooled SMD of post-operative JOAs scores between the anterior and posterior surgery was 0.70 (95% CI from 0.39 to 1.00). The above evidence revealed that the anterior surgery seemed to be more appropriate than the posterior surgery.

Improvement rate (IR)

The IR value was also obtained in order to reflect the improvement in neurological functions of patients and to reduce the possible biases contributed by the JOA scores. Figure 4 revealed the overall pattern of IR with a total of 21 studies and 1,298 patients. Eight studies suggested that the anterior surgery was more effective than the posterior surgery since SMDs in these studies were significantly greater than zero. Although another four studies indicated that the posterior surgery, SMD in these four studies did not significantly different from zero.

We implemented the random-effects model since significant heterogeneity was presented ($l^2 = 74.4\% > 50\%$, *P*-value < 0.0001). The synthesized SMD was 0.48 with a 95% CI from 0.25 to 0.72. As a result, IR also indicated that the anterior surgery was more effective than the posterior surgery.

Blood loss

Figure 5 showed a total of 18 studies that assessed the volume of blood loss between the anterior and posterior surgery. As suggested by six studies, the volume of blood loss between the two approaches did not have significant difference. However, another five of the 12 studies favored the posterior surgery whereas the remaining seven studies supported the anterior surgery with respect to safety. Since l^2 is 94.0% which was significantly larger than 50% and the corresponding *P*-value was less than 0.0001, the random-effects model was implemented. The overall SMD provided by the meta-analysis with a total of 1,138 patients is -0.17 (95% CI from -0.71 to 0.37). Therefore, we concluded that the two surgical approaches yielded similar safety results which was reflected by the volume of blood loss.

Operation time

We also measured and compared the safety of these two surgical approaches using the operation time which was evaluated by 15 articles (**Figure 6A**). Apart from two studies which favored the anterior surgery (less average operation time), a total of ten studies have concluded that the posterior surgery was safer than the anterior surgery. As suggested by the unexpectedly high heterogeneity ($l^2 = 93.9\% > 50\%$, *P*-value < 0.0001), the random-effects model indicated the overall SMD was 0.84 (95% CI from 0.25 to 1.42). Therefore, the posterior surgery was safer than the anterior surgery since it had shorter average operation time.

Complications

Our meta-analysis also investigated the distribution of complications between patients who underwent these two surgical approaches. Among these 13 studies which included a total of 732 subjects, only three studies provided significant statistical results and all of them favored the posterior surgery since the anterior

A Opera	ition t	Ime									
	Ar	nterio	or	Pos	sterio	or					
Study	Mean	SD	Total	Mean	SD .	Tota	I		SMD	95%CI	Weight
Yu 2013 Shibuya 2010 Seng 2013 Lin 2013 Lin 2012 Kristof 2009 Hirai 2011 Huo 2010 Li 2015 Wada 2001 Sakai 2002 Liu 2012 Fang 2013 Fujimori 2013 Iwasaki 2007	155.48 334.88 186.00 124.00 161.00 229.24 211.00 138.64 104.90 264.00 300.30 115.92 178.00 314.00 302.00	17.11 82.58 38.00 47.00 45.00 60.10 55.30 47.30 19.40 65.00 78.60 24.14 31.00 89.90 75.75	29 34 56 27 26 42 39 11 19 23 20 25 54 12 27	192.25 175.00 123.00 125.00 183.84 149.00 108.60 104.80 182.00 183.20 187.78 144.00 128.00 177.00	33.47 60.00 28.00 36.00 34.00 46.62 38.70 28.20 26.20 43.00 41.10 25.01 20.00 60.00 76.25	24 49 24 30 61 47 14 76 24 22 75 56	+ -	<u>+++++++++++++++++++++++++++++++++++++</u>	-1.40 2.26 1.83 0.21 0.90 0.86 1.31 0.77 0.00 1.47 1.86 -2.88 1.30 -2.42 1.63	[-2.01; -0.80] [1.70; 2.82] [1.36; 2.31] [-0.34; 0.76] [0.35; 1.45] [0.45; 1.27] [0.45; 1.59] [-0.50; 0.51] [0.82; 2.12] [1.12; 2.59] [-3.67; -2.09] [0.89; 1.71] [1.39; 3.45] [1.12; 2.14]	6.7% 6.8% 6.8% 6.8% 6.9% 6.9% 6.8% 6.6% 6.6% 6.6% 6.4% 7.0% 5.9% 6.8%
Random effects	model		444			577			0.84	[0.25; 1.42] 100%
Heterogeneity:	l²=93.9%,	tau ² =1.	.243, P	<0.0001				15			
									7		
							-3 -2 -1	012	3		

Favours [posterior] Favours [anterior]

••••••	noalloi							
	Ante	erior	Poste	rior				
Study	Events	5 Total	Events	Total		OR	95%CI	Weight
					·			
Chen 2008	6	14	10	20		0.75	[0.19; 2.96]	8.7%
Zhang 2012	9	20	13	28		0.94	[0.30; 2.99]	9.6%
Chen 2010	12	51	28	75	 .	0.52	[0.23; 1.15]	11.0%
Wang 2008	8	16	2	6		2.00	[0.28; 14.20]	6.6%
Yu 2013	15	29	18	24		0.36	[0.11; 1.16]	9.5%
Huo 2010	4	11	6	14		0.76	[0.15; 3.86]	7.8%
Cabraja 2010	3	39	4	28		0.50	[0.10; 2.44]	7.9%
Edwards 2002	9	13	1	25	·	54.00	[5.30;550.23]	5.5%
Chen 2011	5	22	15	53		0.75	[0.23; 2.38]	9.6%
Li 2015	5	19	0	76	→	58.03	[3.04;1107.68]	4.1%
Lau 2015	4	20	2	35		4.12	[0.68; 24.94]	7.1%
Sakai 2002	5	20	0	22		15.97	[0.82;310.14]	4.1%
Liu 2012	9	25	3	27		4.50	[1.05; 19.22]	8.4%
Random effects	model	299		433	6	1.59	[0.77; 3.29] 100%
Heterogeneity:	P=66.4%, tau	r²=1.072, F	P=0.0004		:			
						_		
Figure 6. The for	est plot of (A	A) operation	on	0	0.1 1 10	1000		
time and (B) com	plications.		Favou	rs [post	erior] Favou	urs [anterior]		

surgery exhibited an increased OR of complications compared to the posterior surgery (**Figure 6B**). However, the overall OR suggested by the random-effects model appeared to be insignificant (OR = 1.59, 95% CI from 0.77 to 3.29) and this trend may be explained by the presence of significant heterogeneity ($I^2 = 66.4\% > 50\%$).

Publication bias

The comparison-adjusted funnel plot is an graphical approach for assessing the presence of publication bias. Since no significant asymmetry patterns were observed in pre-operation

JOA scores, post-operation JOA scores, IR, blood loss, operation time or complications studies associated with these endpoints did not contain significant publication bias (Figure S1).

Discussion

This meta-analysis gathered and researched on the data from 33 studies with 2,910 subjects, who were diagnosed as OPLL or CSM. Either the anterior or posterior surgery was introduced to these patients and our study focused on comparing the effectiveness and

В

Complications

safety between the two surgical approaches. The anterior surgery seemed to be more effective than the posterior surgery with respect to pre-operative JOA scores, post-operative scores and IR values. On the other hand, measurements such as blood loss, operation time and risk of complication were taken into account for the sake of evaluating the safety of these two surgical approaches. Although the posterior surgery appeared to be slightly better than the anterior surgery with respect to blood loss and risk of complications, such a tendency was not statistically significant. Therefore, it is challenging to conclude that the posterior surgery is safer than the anterior surgery due to the lack of sufficient evidence.

The anterior surgery is a type of surgical technique which is operated through the incision of the neck of patients. The centrum is resected using ACCF whereas the intervertebral disc is removed by ACDF. Furthermore, decompression and fusion is implemented by resecting and trimming both centrum and disc. After that, the bone graft from autologous ilium is fused in the drill hole which is located in the intervertebral space [30, 51, 52]. As suggested by higher post-operation JOA scores and IR values, the anterior surgery has positive effects on improving the neurological function of patients. However, this approach is far more complicated than other techniques since the corresponding incision must pass through the skin, the subcutaneous tissue and the platysma so that the fascia space can be separated and the injury of carotid artery and trachea can be prevented. This may explain the fact that the anterior surgery usually takes longer operation time than other surgical techniques [53]. Several complications have been linked with the anterior surgery and they include persistent dysphagia, myelopathy progression and subjacent ankylosis [54].

The posterior surgery which was included in our meta-analysis mainly focused on the laminoplasty and laminectomy. The following procedures are usually implemented in laminoplasty: lamina is partially cut on both sides in order to rebuild the spinal canal and relieve the pressure on the cervical spinal cord [55]. By contrast, laminectomy is a popular back surgery which involves the process of lamina removal and the resection of bone spurs with ligaments so that the spinal cord and nerves can be decompressed [56]. Although the posterior surgery may not be as effective as the anterior surgery, it is simple to be operated and hence it is considered as a safer approach due to reduced blood loss volume, operation time and risk of complications. Thus, the posterior surgery is widely used for patients with poor tolerance or those who need multi-level treatment.

This meta-analysis compared the efficacy and safety between the anterior and posterior surgery for patients with OPLL or CSM through pooling data from individual studies. Some limitations contained in this study must be mentioned: (i) studies on CSM were included and they may cover other types of CSM other than OPLL and this was performed in order to increase the sample size and statistical power; (ii) we imputed some data if some key information was missing and some estimators may be biased (iii) We ignored the detailed modality of each surgery which may be a confounding factor or effect modifier for the overall conclusions in order to accommodate the nature of the approach of meta-analysis.

Conclusively, the anterior surgery exhibited more effectiveness than the posterior approach for managing OPLL patients. The posterior surgery slightly safer than the anterior surgery, but more evidence is demanded in order to conclude statistical significance. Apart from this, the selection of surgical techniques for OPLL patients should accommodate patients' physical conditions in order to maximize their efficacy and safety.

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Disclosure of conflict of interest

None.

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Figure S1. The funnel plot of the six outcomes. A: JOA score-before operation; B: JOA score-post operation; C: Improvement rate; D: Blood loss; E: Operation time; F: Complications.

1			0	-					
		Risk of Bias Applicability							
QUADAS-2	(1)	(2)	(3)	(4)	(5)	(6)	(7)		
Studid	Subjbias	Testbias	Refbias	Diagbias	Subjapp	Testapp	Refapp	Qscore	
Chen, 2008	Yes	No	Yes	Yes	Yes	Yes	Yes	6	
Liu, 2010	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes	5	
Zhang, 2012	Yes	No	Yes	Yes	Yes	Yes	Yes	6	
Wu, 2009	Yes	Yes	Yes	Yes	No	Yes	Unclear	5	
Chen, 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7	
Wang, 2008	Yes	Unclear	Yes	Yes	Yes	No	Yes	5	
Yu, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7	
Shibuya, 2010	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes	5	
Seng, 2013	Yes	Yes	Yes	No	Yes	Yes	No	5	
Sah, 2012	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	6	
Liu, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7	
Lin, 2013	No	Yes	Yes	Yes	Yes	Yes	Yes	6	
Lin, 2012	Yes	Yes	Yes	No	Yes	Yes	Yes	6	
Kristof, 2009	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	6	
Jain, 2005	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	6	
Hirai, 2011	Yes	Unclear	Yes	Yes	No	Yes	Yes	5	
Ghogawala, 2011	No	Yes	Yes	No	Yes	Yes	Yes	5	
Huo, 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7	
Fehlings, 2013	Yes	Yes	No	No	Yes	Yes	Yes	5	
Cabraja, 2010	Yes	No	Yes	Yes	Yes	Yes	Yes	6	
Edwards, 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7	
Chen, 2011	Unclear	No	Yes	Yes	Yes	Yes	Yes	5	
Li, 2015	Yes	Yes	Yes	Yes	Yes	No	Yes	6	
Lau, 2015	Yes	Unclear	No	Yes	Yes	Yes	Yes	5	
Kim, 2015	No	Yes	Yes	Yes	Yes	Yes	Yes	6	
Wang, 2006	Yes	No	Yes	Yes	Yes	Yes	Yes	6	
Wada, 2001	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7	
Sakai, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7	
Masaki, 2007	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	6	
Liu, 2011	No	Yes	Yes	Yes	Yes	Yes	Yes	6	
Fang, 2013	Yes	Yes	No	Yes	Yes	No	Yes	5	
Fujimori, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7	
Iwasaki, 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7	

 Table S1. The quality of all included studies using QUADAS-2