

# Effects and Safety of Lumbar Fusion Techniques in Lumbar Spondylolisthesis: A Network Meta-Analysis of Randomized Controlled Trials

Global Spine Journal  
2022, Vol. 12(3) 493–502  
© The Author(s) 2021  
Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/2192568221997804  
journals.sagepub.com/home/gsj  


Yi-No Kang, MA<sup>1,2,3,4</sup>, Yu-Wan Ho, MD<sup>5</sup>, William Chu, MD, PhD<sup>6</sup>,  
Wen-Shiang Chou, MD<sup>6</sup>, and Shih-Hao Cheng, MD<sup>6,7</sup> 

## Abstract

**Study Design:** Network meta-analysis of randomized controlled trials.

**Objectives:** Lumbar spondylolisthesis is a common indication for spinal fusion. Lumbar interbody fusion (LIF) is popular method to achieve arthrodesis, but previous syntheses usually used head-to-head comparison of 2 surgical methods, and no of them pooled analysis with high-quality. This network meta-analysis of randomized controlled trials was carried out to simultaneously compare fusion techniques in the treatment of lumbar spondylolisthesis.

**Methods:** Three databases were searched for randomized controlled trials (RCTs) on this topic. After critical appraisal, fusion rate, overall adverse events, operative time, Oswestry Disability Index, and pain were extracted for analysis. We conducted network meta-analysis using contrast-based method. Primary outcomes were reported as risk ratio (RR) with 95% confidence interval (CI).

**Results:** Fifteen RCTs (n = 992) met our eligibility criteria. The RCTs treated patients posterolateral fusion (PLF), posterior LIF (PLIF), transforaminal LIF (TLIF), minimally invasive (MIS) TLIF, extreme lateral LIF (XLIF), and circumferential fusion. The pooled estimate showed that circumferential fusion led to significantly higher fusion rate than PLF (RR = 2.15, 95%CI: 1.41–3.28), PLIF (RR = 2.11, 95%CI: 1.38–3.22), TLIF (RR = 2.13, 95%CI: 1.39–3.27), MIS-TLIF (RR = 2.13, 95%CI: 1.35–3.35), and XLIF (RR = 2.01, 95%CI: 1.25–3.22). Moreover, circumferential fusion exhibited the best balance in probability between fusion rate and adverse event rate. No evidence showed inconsistency or small-study effect in the results.

**Conclusions:** Collectively, circumferential fusion might be worth to be recommended because it exhibits the best balance between fusion rate and overall adverse event. PLF is still an inferior procedure and requires shorter operative time.

## Keywords

lumbar spondylolisthesis, anterior lumbar interbody fusion, posterior lumbar interbody fusion, transforaminal lumbar interbody fusion

## Abbreviations

ALIF, anterior lumbar interbody fusion; CI, confidence interval; LIF, lumbar interbody fusion; MIS, minimally invasive; ODI, Oswestry disability index; OLIF, oblique lumbar interbody fusion; PLF, posterolateral fusion; PLIF, posterior lumbar interbody fusion; TLIF, transforaminal lumbar interbody fusion; RCT, randomized control trial; RR, risk ratio; SMD, while standardized mean difference; SUCRA, surface under the cumulative ranking curve; WMD, weighted mean difference; XLIF, extreme lateral lumbar interbody fusion

<sup>1</sup> Evidence-Based Medicine Center, Wan Fang Hospital, Medical University Hospital, Taipei

<sup>2</sup> Research Center of Big Data and Meta-analysis, Wan Fang Hospital, Taipei Medical University, Taipei

<sup>3</sup> Cochrane Taiwan, Taipei Medical University, Taipei

<sup>4</sup> Institute of Health Policy & Management, College of Public Health, National Taiwan University, Taipei

<sup>5</sup> Department of Emergency Medicine, Taipei Medical University Hospital, Taipei

<sup>6</sup> Department of Orthopedics, Cheng Hsin General hospital, Taipei

<sup>7</sup> Department of Orthopedics, Wan Fang Hospital, Medical University Hospital, Taipei

## Corresponding Author:

Shih-Hao Cheng, Department of Orthopedics, Cheng Hsin General Hospital, Taipei.

Email: franchpaladin@gmail.com



Creative Commons Non Commercial No Derivs CC BY-NC-ND: This article is distributed under the terms of the Creative Commons Attribution-Non Commercial-NoDerivs 4.0 License (<https://creativecommons.org/licenses/by-nc-nd/4.0/>) which permits non-commercial use, reproduction and distribution of the work as published without adaptation or alteration, without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

## Introduction

Lumbar spondylolisthesis is a common adult spinal disorder.<sup>1-3</sup> Although many patients are asymptomatic and lumbar spondylolisthesis is found incidentally,<sup>4,5</sup> the disease can lead to low back pain and radicular pain. Most of the patients can be managed conservatively with spinal brace, drugs, physical therapy, and epidural steroid injection.<sup>6</sup> However, patients with refractory symptoms who do not respond well to the abovementioned treatments still require surgical managements. Among the surgical procedures indicated for spondylolisthesis, spinal fusion after neural element decompression is the standard technique. This procedure has been used for a long period and demonstrates satisfactory outcome.<sup>7,8</sup> Many options are available to perform lumbar spinal fusion, and posterolateral fusion (PLF) has been considered the gold standard for decades.<sup>9,10</sup> Lumbar interbody fusion (LIF) with bone grafts or cages became popular recently. The proposed benefits of interbody fusion include restoration of spinal alignment, indirect decompression of the neural foramen, and increasing fusion rate.<sup>11,12</sup> Anterior LIF (ALIF), posterior lumbar interbody fusion (PLIF), and transforaminal interbody fusion (TLIF) are proved to be effective methods.<sup>13-15</sup>

Recently, many minimally invasive surgical (MIS) procedures were introduced, such as MIS-PLIF, MIS-TLIF, and oblique LIF (OLIF). These MIS are associated with minor trauma to the bone and soft tissue, lesser blood loss, and shorter hospital stay, but their safety and efficacy are still unclear.<sup>16-19</sup> Despite the surgical techniques in the treatment of lumbar spondylolisthesis, a high-quality, pooled evidence on the topic is still lacking. Thus, this network meta-analysis of randomized controlled trials (RCTs) was carried out to compare fusion techniques in the treatment of lumbar spondylolisthesis. To the best of our knowledge, this is the first network meta-analysis focusing on the surgical methods to treat lumbar spondylolisthesis.

## Methods

This systematic review with network meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for reporting methods and results. The primary eligibility criteria of studies were as follows: (a) enrolled patients with lumbar spondylolisthesis, (b) treated patients LIF techniques, and (c) employed an RCT design. The exclusion criteria of studies were as follows: (a) recruited patients with spondylolisthesis and other disk disorders without stratification, (b) compared fusion procedures with decompression alone without fusion, (c) did not compare LIF technique to surgical intervention or other LIF technique, and (d) had gray literature without details about methods and results.

## Data Sources

Databases of Embase, PubMed (including MEDLINE), and Web of Science were searched for potential references using

the following relevant terms: spondylolisthesis, PLIF, TLIF, lateral LIF, extreme lateral LIF (XLIF), OLIF, and ALIF. To increase sensitivity, the Boolean operator “OR” was applied to combine relevant terms of fusion techniques, and the Boolean operator “AND” was used to identify intersection of search results of spondylolisthesis and fusion techniques. The primary search strategy of fusion techniques for spondylolisthesis was built in PubMed. Although the search strategy did not use any filters for publication year, age, sex, journal category, or language, we restricted studies to human by using the Boolean operator “NOT” animal [MeSH Terms: noexp]. The final search was done in April 2020 (Supplementary File 1).

## Evidence Selection

To identify potential references from the databases, 2 authors imported references into EndNote software X9 for further screening. They independently screened and checked titles and abstracts for eligibility. Then, they retrieved the full texts for further review. All team members made the final judgment of the evidence selection if the 2 authors had inconsistency in choosing articles.

## Data Extraction

The 2 authors also independently extracted and double-checked information and data from each trial. They listed the first author's family name, publication year, study region, fusion technique, age, sex, spondylolisthesis type, and disease grade. They extracted events, sample size for fusion rate and overall adverse event, and mean, standard deviation, and sample size for operative time, Oswestry Disability Index (ODI) score, and pain score from the included RCTs. Overall adverse event in the included trials mainly involved nerve injury, infection, cage migration, dura tear, screw loosening, and screw breaking. If the trials presented percentage for fusion rate or adverse event, these events were converted according to the sample size.

## Quality Assessment

All included RCTs underwent quality assessment, and the 2 authors evaluated the risk of bias by using the Cochrane Risk of Bias Tool. It is a common tool for RCT appraisal and covered randomization generation, allocation concealment, blinding (we mainly assessed blinding of patients and assessor because this topic cannot blind to surgeon), incomplete outcome data, selective report, and other source of bias. We reported overall risk of bias according to rules as follows: (a) if any bias was high risk, overall risk of bias should be high risk; (b) if any bias was unclear and no high risk of bias, overall risk of bias was unclear; and (c) if all bias were low risk, overall risk of bias was low risk. Discrepancy on risk of bias appraisal was resolved by discussion.

## Data Synthesis and Analysis

In this study, the primary outcomes were fusion rate and overall adverse event rate (dichotomous variables); thus, risk ratio (RR) was used to present pooled estimate. Secondary outcomes were operative time, ODI score, and pain score (continuous variables). Pooled operative time and ODI were presented in weighted mean difference (WMD), while standardized mean difference (SMD) was used for pooled estimate of pain score because of the heterogeneity of scales used for pain measurement across RCTs. We also presented 95% confidence interval (CI) with effect sizes.

Most outcomes, except pain score, were pooled using contrast-based network meta-analysis, and inconsistency and small-study effects were assessed. We chose the design-by-treatment interaction model to detect inconsistency because 2-arm and 3-arm trials were included in our synthesis and contributed to network meta-analysis. Adjusted funnel plot and Egger's regression intercept with centralized effect size and standard error were used to analyze small-study effect. Moreover, we conducted surface under the cumulative ranking (SUCRA) to clarify the probability of successful fusion and adverse events among PLF, PLIF, TLIF, MIS-TLIF, XLIF, and circumferential fusion. The SUCRA showed the probability of each fusion technique in ranking hierarchy and demonstrated a value of the surface under the line of cumulative ranking with mean rank. When the SUCRA value of a fusion technique was close to 1, the fusion technique had a higher probability of having better outcome. An optimal fusion technique ideally has well-balanced probabilities of higher fusion rate and lower adverse event rate; we further presented cluster plots using the SUCRA values of the fusion rate and overall adverse events. Moreover, meta-regression of proportion of isthmic lumbar spondylolisthesis was conducted under consistency model for testing the effect of subtype of lumbar spondylolisthesis on the pooled result. Thus, option "regression" was used under command "network meta" in STATA.

Because pain score data was only available from trials comparing PLF and PLIF, a network meta-analysis was unnecessary. Pain score was pooled by using pairwise meta-analysis according to the DerSimonian and Laird method. We presented I-square to understand heterogeneity among the pooled trials. When the I-square was higher than 50%, the pooled estimate of the pain score was heterogeneous. All the abovementioned analyses were carried out by STATA version 14 (StataCorp LP, College Station, Texas).

## Results

We found 3832 references, which was composed of 3831 references from Embase ( $k = 1496$ ), PubMed ( $k = 1067$ ), and Web of Science ( $k = 1268$ ). Other references were found by reviewing the reference lists of relevant studies. We used the function "Find duplicates" in EndNote software to remove duplicates ( $k = 1222$ ). Irrelevant references were routed out after screening of the title and abstract ( $k = 2567$ ), and we retrieved full

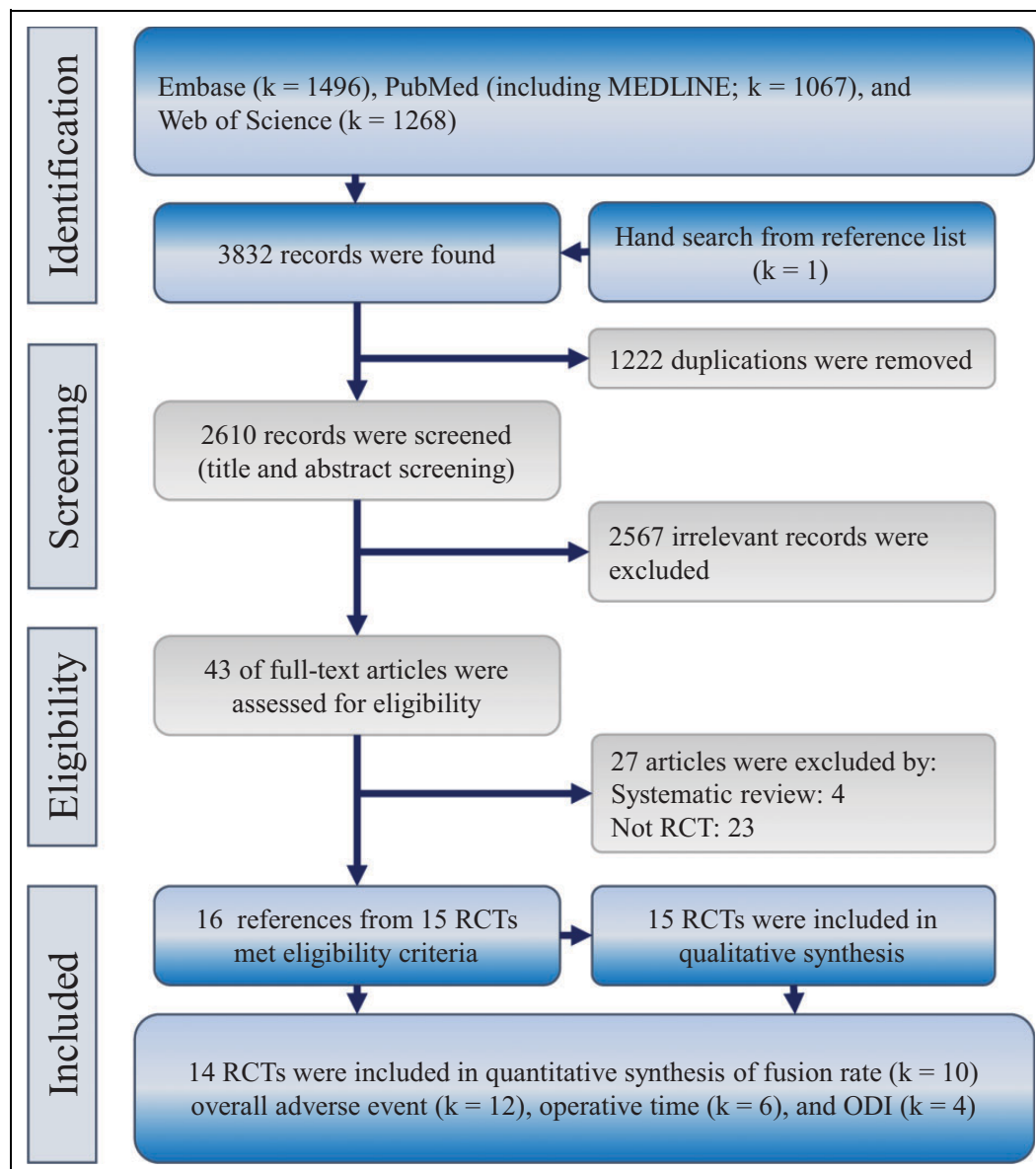
texts for the remaining references ( $k = 43$ ). Finally, 16 references from 15 RCTs met our eligibility criteria, and all of them were included in this synthesis (Figure 1).<sup>18,20-34</sup>

## Characteristics and Quality of Included Studies

This synthesis included 15 RCTs from China ( $k = 3$ ),<sup>23,27,34</sup> Egypt ( $k = 1$ ),<sup>20</sup> France ( $k = 1$ ),<sup>22</sup> India ( $k = 1$ ),<sup>28</sup> Iran ( $k = 4$ ),<sup>21,24-26</sup> Japan ( $k = 1$ ),<sup>18</sup> Korea ( $k = 1$ ),<sup>30</sup> Romania ( $k = 1$ ),<sup>33</sup> Turkey ( $k = 1$ ),<sup>31</sup> and USA ( $k = 1$ ),<sup>29,32</sup> between 2005 and 2019. These studies recruited 992 patients with lumbar spondylolisthesis. The patients underwent PLF, PLIF, TLIF, MIS-TLIF, XLIF, and circumferential fusion. Beside of traditional PLF and minimal invasive procedures, combination surgical strategy such as circumferential fusion were investigated, wherefore the present study also included RCTs that implemented circumferential fusion on spondylolisthesis. For broader definition, even TLIF with PLF and posterior instrumentation can be considered circumferential fusion although a specific definition of circumferential fusion is usually considered ALIF with posterior instrumentation. Circumferential fusion in the present synthesis involved combination of TLIF and PLF. The mean age in each study arm ranged from 41.4 to 68.2 years according to the available information. Further information about gender, type of spondylolisthesis, and grade are presented in Table 1. Most trials seemed to be high risk of bias due to inappropriate blinding to patients or assessor; and no trial was low risk of bias.

## Primary Outcome

The primary outcomes were fusion rate and overall adverse event rate. A total of 10 RCTs contributed to a 6-node network meta-analysis of the fusion rate (Figure 2A).<sup>20,22,23,25,28-31,33,34</sup> The network involved 783 cases with spondylolisthesis treated by PLF ( $n = 273$ ), PLIF ( $n = 292$ ), TLIF ( $n = 102$ ), MIS-TLIF ( $n = 59$ ), XLIF ( $n = 27$ ), and circumferential fusion ( $n = 30$ ). Pooled result showed that with PLF as the reference, PLIF (RR 1.02, 95% CI 0.96 to 1.09), TLIF (RR 1.01, 95% CI 0.93 to 1.10), MIS-TLIF (RR 1.01, 95% CI 0.85 to 1.20), and XLIF (RR 1.07, 95% CI 0.87 to 1.33) did not lead to significant difference (Figure 3A). Moreover, no significant difference was found among PLIF, TLIF, MIS-TLIF, and XLIF. However, circumferential fusion presented significantly higher fusion rate than PLF (RR 2.15, 95% CI 1.41 to 3.28), PLIF (RR 2.11, 95% CI 1.38 to 3.22), TLIF (RR 2.13, 95% CI 1.39 to 3.27), MIS-TLIF (RR 2.13, 95% CI 1.35 to 3.35), and XLIF (RR 2.01, 95% CI 1.25 to 3.22). These results were also observed in the SUCRA (Supplementary File 2). Design-by-treatment interaction model did not show significant inconsistency in the network meta-analysis of the fusion rate (Chi-square = 1.39;  $P = 0.50$ ; Supplementary File 3). Funnel plot (Figure 4A) and Egger's test showed that small-study effect was not significant in the pooled estimate of the fusion rate ( $t = -0.10$ , 95% CI  $-0.85$  to  $0.78$ ; Supplementary File 4). Subtype of lumbar spondylolisthesis did not show statistical



**Figure 1.** Flowchart of this systematic review with network meta-analysis of prospective studies. ODI, Oswestry Disability Index; RCTs, randomized clinical trials.

significance in the consistency model of fusion rate (Supplementary File 5).

Another primary outcome was safety of fusion techniques, and 12 RCTs formed a 6-node network meta-analysis of the overall adverse event (Figure 2B).<sup>20,22-25,27-31,33,34</sup> The network involved 878 cases with spondylolisthesis treated by PLF (n = 322), PLIF (n = 313), TLIF (n = 102), MIS-TLIF (n = 59), XLIF (n = 27), and circumferential fusion (n = 55). Although no significant difference existed among the 6 fusion techniques (Figure 3B), some pooled estimates raised clinical concerns. For instance, some estimates showed RR >1.5 or <0.5. To foster understanding on the safety of the 6 techniques, we performed SUCRA, and MIS-TLIF had the highest probability in preventing adverse event (mean rank = 1.9; SUCRA

= 82.6), followed by PLF (mean rank = 3.2; SUCRA = 55.2), circumferential fusion (mean rank = 3.3; SUCRA = 53.3), XLIF (mean rank = 4.0; SUCRA = 39.8), TLIF (mean rank = 4.1; SUCRA = 37.8), and PLIF (mean rank = 4.4; SUCRA = 3.13; Supplementary File 6). Design-by-treatment interaction model showed no significant inconsistency in the network meta-analysis of the overall adverse event (Chi-square = 0.06;  $P = 0.97$ ; Supplementary File 7). Egger's test indicated that the pooled estimate may be affected by the small-study effect ( $t = 2.58$ , 95% CI 0.24 to 2.86), but Begg's test showed no significance ( $z$  value = 1.75,  $P = 0.09$ ; Supplementary File 8). Moreover, contour-enhanced funnel plot depicted that the possibly missed trial is found on upper right of the funnel plot, and this situation is not a typical asymmetry of small-study effect

**Table 1.** Characteristics of the Included Randomized Controlled Trials.

Study	Aria	Follow-up (month)	Procedure	Mean age	Male/Female	Isthmic/Degen.	Grade I/II/III/IV	Overall bias
Fei et al. 2005	China	>24	PLF	53	8/16	7/17	17/7/0/0	High
			PLIF	56	8/13	5/16	15/6/0/0	
Inamdar et al. 2006	India	12	PLF	44.7	NA	5/5	NR	High
			PLIF	41.4	NA	5/4	NR	
Cheng et al. 2009	China	48	PLF	48	36/32	29/41	Overall:	High
			PLIF	49	39/31	33/41	62/76/0/0	
Ahmet et al. 2011	Turkey	24	PLF	53.4	9/16	25/0	15/10/0/0	Unclear
			PLIF	51.7	8/17	25/0	13/12/0/0	
Farrokhi et al. 2012	Iran	6	PLF	49.66	10/30	40/0	NR	Unclear
			PLIF	50.35	9/31	40/0	NR	
Mukai et al. 2013	Japan	12	MIS-PLIF	68.5	NA	0/20	NR	High
			PLIF	62.3	NA	0/20	NR	
Lee et al. 2014	Korea	24	PLF	53.4	21/18	39/0	34/4/1/0	Unclear
			PLIF	53.7	23/19	42/0	35/6/1/0	
Alijani et al. 2015	Iran	12	PLF	55	9/42	14/37	35/16/0/0	Unclear
			PLIF	52	10/41	15/36	21/30/0/0	
Fariborz et al. 2016	Iran	6	PLF	NA	16/14	NA	30/0/0/0	High
			PLIF	NA	18/12	NA	30/0/0/0	
			TLIF	NA	15/15	NA	30/0/0/0	
Challier et al. 2016	France	6	PLF	63	9/21	0/30	NR	High
			Circ.	66	9/21	0/30	NR	
Etemadifar et al. 2016	Iran	NA	PLF	53.4	11/14	25/0	17/8/0/0	High
			Circ.	51.7	9/16	25/0	19/5/1/0	
Yang et al. 2016	China	>3	PLIF	42.7	14/20	34/0	11/20/3/0	High
			TLIF	44.1	13/19	32/0	10/19/3/0	
Issacs et al. 2016	USA	24	XLIF	63	13/16	0/29	28/1/0/0	High
			MIS-TLIF	64	11/15	0/26	21/5/0/0	
Serban et al. 2017	Romania	12	TLIF	50.12	17/23	28/12	20/20/0/0	High
			MIS-TLIF	51.3	16/24	26/14	19/21/0/0	
AbdelkAder et al. 2019	Egypt	24	PLF	44.1	5/15	20/0	NR	Unclear
			PLIF	44.1	6/14	20/0	NR	

Circ., circumferential; Degen., degenerative; MIS, minimally invasive; NR, no report; PLIF, posterior lumbar interbody fusion; PLF, posterolateral fusion; TLIF, transforaminal lumbar interbody fusion; XLIF, extremely lateral lumbar interbody fusion.

(Figure 4B). Trend and direction of comparison of PLIF and PLF did not affected after proportion of isthmic lumbar spondylolisthesis put into consistency model although the proportion showed statistical significance in the consistency model of adverse event rate (Supplementary File 9).

We further explored the balance of effect and safety among PLF, PLIF, TLIF, MIS-TLIF, XLIF, and circumferential fusion by cluster plots of the fusion rate and overall adverse (Figure 5). Circumferential fusion exhibited the best balance when we restricted to 2 clusters, and it still showed better balanced probability between fusion rate and adverse event rate when the optimal number of clusters was 3 with clustering gain of approximately 460.53. However, only 2 trials used circumferential fusion, and it was only compared with PLF. Therefore, circumferential fusion should be recommended with caution for patients with lumbar spondylolisthesis.

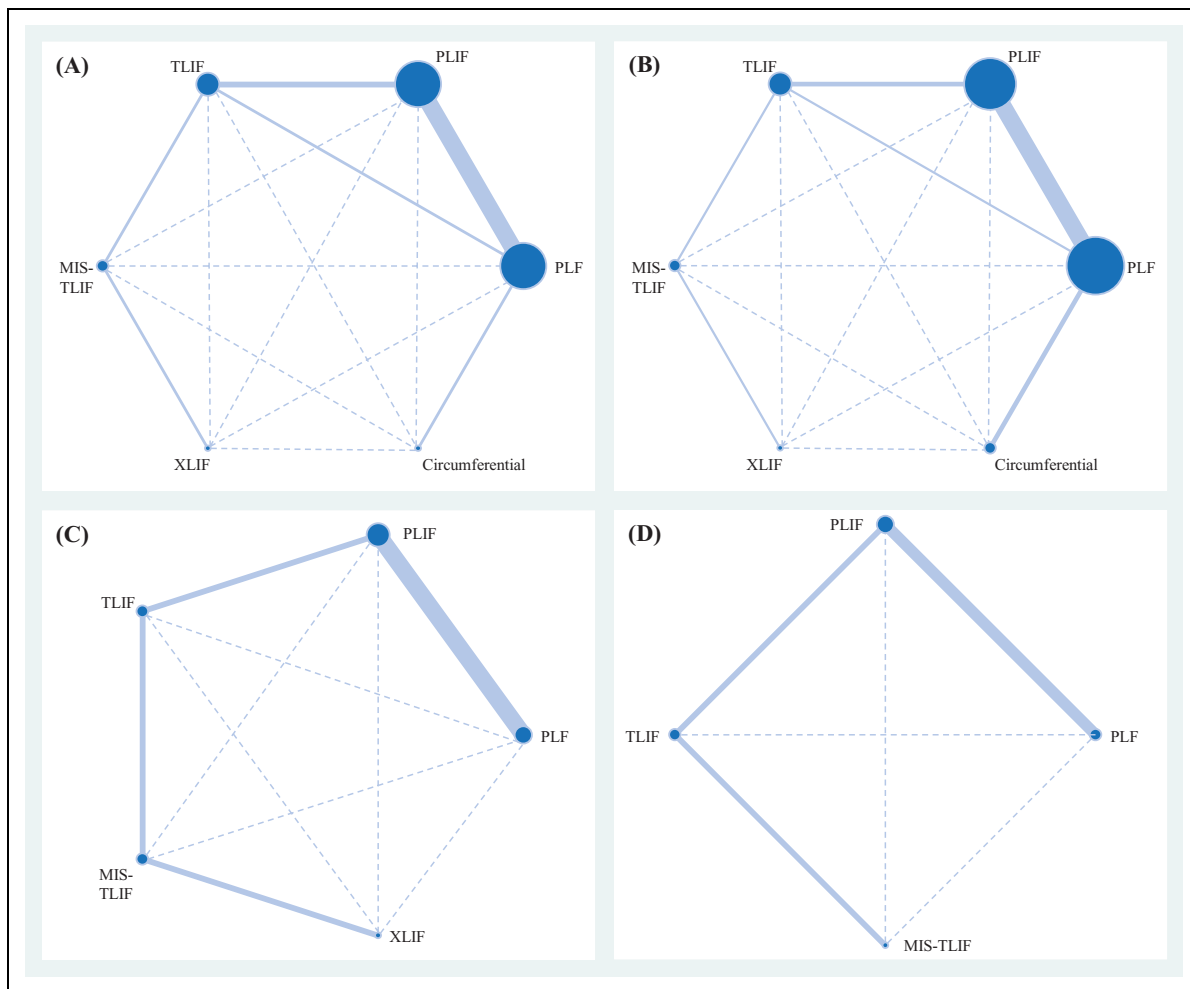
## Secondary Outcome

The secondary outcomes were operative time, ODI score, and pain score. Six of the included RCTs ( $n = 347$ ) reported

operative time,<sup>27,29-31,33,34</sup> and the data came from PLF ( $n = 59$ ), PLIF ( $n = 128$ ), TLIF ( $n = 76$ ), MIS-TLIF ( $n = 65$ ), and XLIF ( $n = 19$ ) (Figure 2C). Pooled estimate of operative time showed that PLIF has longer operative time than PLF (WMD = 49.64, 95% CI 4.40 to 94.88). TLIF, MIS-TLIF, and XLIF showed longer operative time than PLF, though the pooled estimates were non-significant (Figure 3C). Inconsistency test cannot be carried out because the available data did not form any loop. Funnel plot and Egger's test showed that the small-study effect was not significant in the pooled estimate of operative time ( $t = -0.67$ , 95% CI  $-17.71$  to  $10.81$ ; Supplementary File 10). Although proportion of subtype of lumbar spondylolisthesis showed statistical significance in the consistency model of operative time between PLIF and PLF, trend and direction of the comparison did not affected after the proportion put into the network meta-analysis model (Supplementary File 11)

Patients' subjective outcomes were ODI, back pain, and leg pain. Data on ODI was available from 4 RCTs ( $n = 329$ ),<sup>21,30,33,34</sup> and the available data can form a 4-node network meta-analysis with PLF ( $n = 90$ ), PLIF ( $n = 127$ ),





**Figure 2.** Network geometry of the consistency model of (A) the fusion rate, (B) overall adverse event, (C) operative time, and (D) Oswestry Disability Index. CI, confidence interval; MIS, minimally invasive; PLF, posterolateral fusion; PLIF, posterior lumbar interbody fusion; TLIF, transforaminal lumbar interbody fusion; XLIF, extremely lateral lumbar interbody fusion.

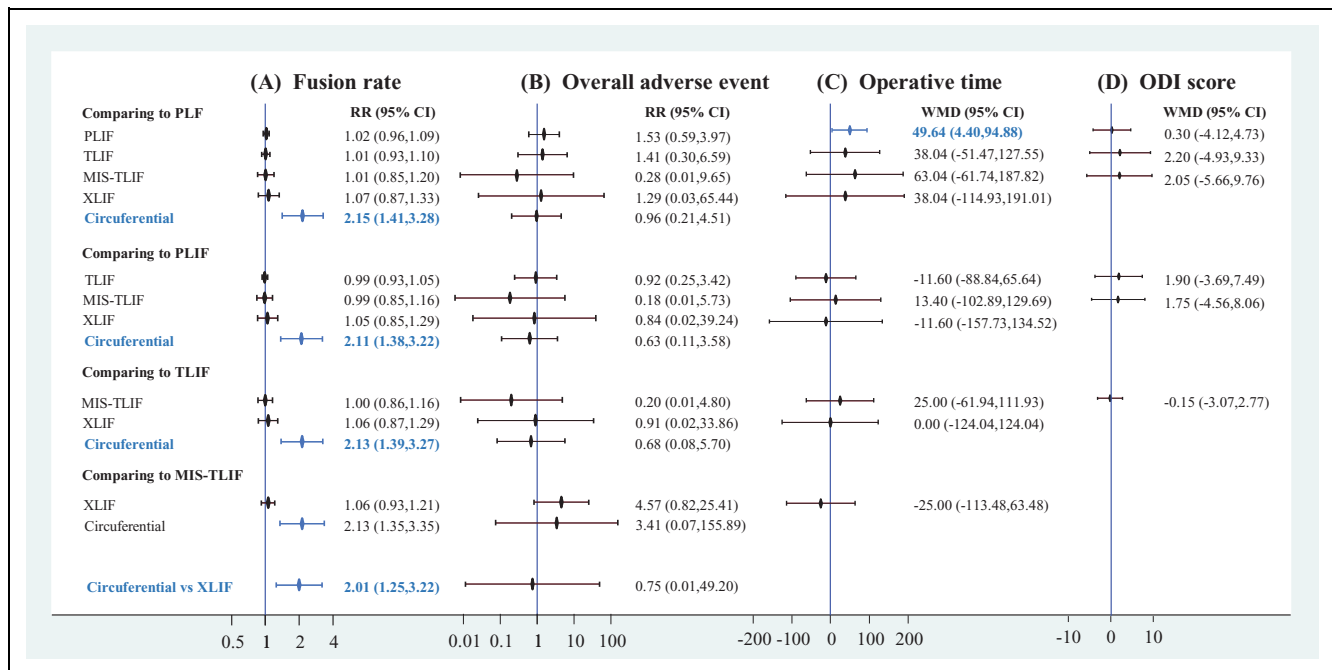
TLIF ( $n = 72$ ), and MIS-TLIF ( $n = 40$ ) (Figure 2D). The network meta-analysis showed no significant difference in the ODI between every pairwise comparison of fusion techniques (Figure 3D). Because there was no loop among the 4 fusion techniques, inconsistency test cannot be carried out. Funnel plot and Egger's test showed that the small-study effect was not significant in the pooled estimate of ODI ( $t = -1.23$ , 95% CI  $-2.10$  to  $1.16$ ; Supplementary File 12). Subtype of lumbar spondylolisthesis did not show statistical significance in the consistency model of ODI (Supplementary File 13). Pain score data was available for comparison of PLF and PLIF in 5 RCTs.<sup>20,26,28,30,31</sup> All the 5 RCTs reported score for back pain ( $n = 271$ ), and 4 of them presented leg pain ( $n = 251$ ).<sup>20,26,30,31</sup> Given the heterogeneity of scales to determine pain score across the trials, data was standardized in the meta-analysis. Pooled estimate showed no difference in back pain (SMD =  $-0.28$ , 95% CI:  $-0.82$  to  $0.25$ , I-square = 77.3%) and leg pain (SMD =  $-0.06$ , 95% CI:  $-0.19$  to  $0.31$ , I-square = 2.5%) between PLF and PLIF (Supplementary File 14).

## Discussion

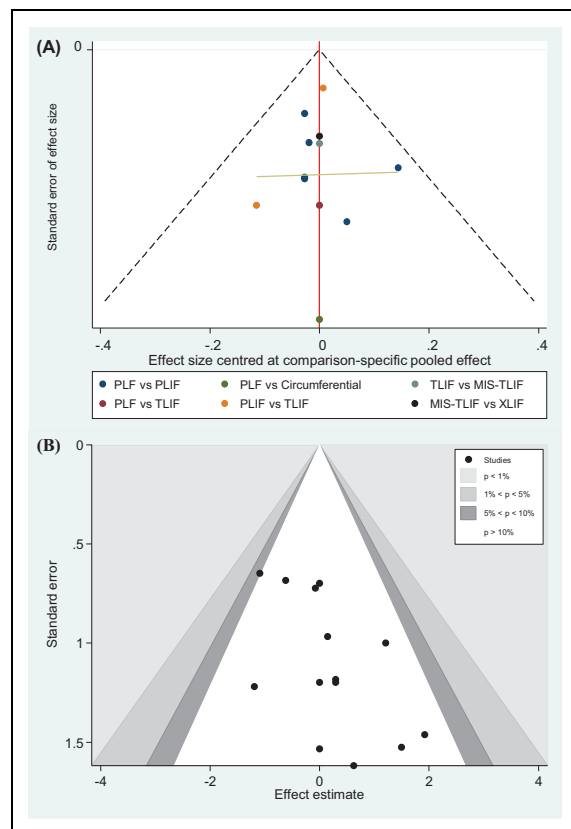
### Key Findings

Our study revealed that circumferential fusion had the highest fusion rate among the procedures. For other approaches, no significant difference was found in the fusion rate or complications. However, MIS-TLIF showed a trend of lower complication rate.

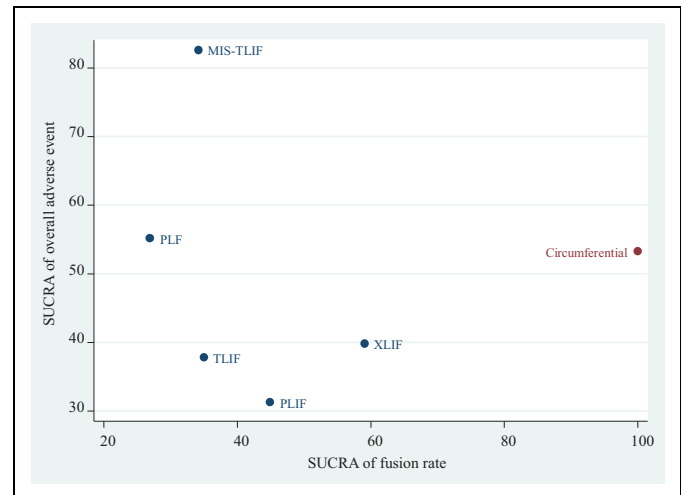
Spondylolisthesis is a common indication for spinal fusion after failed conservative treatment. According to Wiltse classification, spondylolisthesis can be further divided into 6 types, while the isthmic type and degenerative type are present in most of the patients.<sup>35</sup> Although the patient population and common anatomic location are different, the symptoms and management are similar. As a result, we did not analyze the outcome of these 2 types separately. On the contrary, we ruled out the articles that enrolled patients other than those with spondylolisthesis. Spondylosis, low back pain, spinal stenosis, and degenerative disk disease without spondylolisthesis are



**Figure 3.** Forest plots of (A) the fusion rate, (B) overall adverse event, (C) operative time, and (D) Oswestry Disability Index. CI, confidence interval; MIS, minimally invasive; PLF, posterolateral fusion; PLIF, posterior lumbar interbody fusion; RR, risk ratio; TLIF, transforaminal lumbar interbody fusion; XLIF, extremely lateral lumbar interbody fusion.



**Figure 4.** Funnel plots of (A) the fusion rate and (B) overall adverse event. MIS, minimally invasive; PLF, posterolateral fusion; PLIF, posterior lumbar interbody fusion; TLIF, transforaminal lumbar interbody fusion; XLIF, extremely lateral lumbar interbody fusion.



**Figure 5.** Cluster plot for the surface under the cumulative ranking of fusion rate and overall adverse event. MIS, minimally invasive; PLF, posterolateral fusion; PLIF, posterior lumbar interbody fusion; TLIF, transforaminal lumbar interbody fusion; XLIF, extremely lateral lumbar interbody fusion.

excluded from our study because there are fundamental difference between these degenerative disease and spondylolisthesis and there is a need to discuss then independently. Notably, Mukai et al. compared patients who underwent PLIF to MIS-PLIF.<sup>18</sup> Although the studies were enrolled by systemic review, we did not include the data into the pooled analysis because the definition of MIS-PLIF is unclear, which may cause confusion. Some authors defined MIS-PLIF using wound length, while

others used preservation of paraspinal muscle attachment to differentiate it with traditional PLIF.<sup>18,36</sup> Although only a proportion of the patients was grouped randomly, Sembrano et al. discussed XLIF in treating lumbar spondylolisthesis,<sup>32</sup> so we included the data in the pooled analysis.

In our review, the fusion rate is selected as the primary outcome in most studies. Some authors claimed that solid fusion is not related with better clinical symptoms,<sup>37-39</sup> but other studies revealed that solid fusion may have inferior outcome accompanied with pseudoarthrosis.<sup>40-42</sup> In the present study, the circumferential fusion procedure can reach the highest fusion rate, while other approaches revealed similar fusion rate. This is in line with our expectation that combined PLF and interbody fusion can facilitate solid bony union. Unfortunately, the clinical outcome and operative time of circumferential fusion is not available for comparison; thus, we cannot determine whether the procedure is more time-consuming or superior to other techniques clinically. In addition to surgical method, many other factors may affect the success of fusion, such as the type of graft, patient age, comorbidities, smoking, and fusion levels. Despite these factors, the heterogeneity is acceptable throughout the study ( $I^2 < 50\%$ ); thus, we believed that our conclusion is convincing. Another outcome is the postoperative complication rate. All procedures showed similar complication rate without significant difference, but SUCRA revealed higher recommendation for MIS-TLIF. Similar finding was mentioned in the study by Wu et al. and Khan et al.<sup>43,44</sup> Khan et al. explained the phenomenon with surgeon learning curve and maturation of the technique. Generally, MIS is usually more technique demanding with a steeper learning curve than traditional open surgery. However, we believed that the surgeons who performed MIS-TLIF are experienced and familiar with the procedure. Thus, the conclusion can be applied only to mature operators who have sufficient experience of the approach. Among the procedures, PLF seems to be the most time-saving one because the procedure eliminates intervertebral disk removal, endplate preparation, and cage insertion.

### Comparison With Previous Syntheses

In our literature review, many systemic reviews and meta-analysis discussed different fusion methods for spondylolisthesis separately. Ye et al. compared PLIF with PLF and showed higher fusion rate for PLIF, but their study included not only RCTs but also prospective and retrospective studies.<sup>45</sup> Cho et al. compared ALIF with other approaches simultaneously and concluded better restoration of spinal alignment with ALIF. However, the study did not discuss the fusion rate, and the quality of the evidence is not strong.<sup>46</sup> Kwon et al. found that circumferential fusion can achieve higher fusion rate than anterior or posterior procedure alone in the treatment of isthmic spondylolisthesis.<sup>10</sup> Liu et al. also concluded that circumferential fusion improves fusion rate compared with PLF and that the complication rate is comparable.<sup>47</sup> Our research also supports the use of circumferential fusion.

### Limitation

This study has some limitations. First, we included 15 RCTs, yet only one RCT used XLIF and none of them discussed OLIF and ALIF. As a result, based on current evidence, we cannot give recommendation for these 2 procedures even though they showed promising result in non-RCT studies.<sup>48-50</sup> With regard to LIF procedures, direct and guided strategies are discussed in recent years, while they are out of range of our study. Moreover, it seems to appear to be a lack of no randomized controlled trial on direct LIF or guided LIF for spondylolisthesis. They are worth further studies in the future. In addition to limitations on evidence of lumbar fusion techniques, outcome limitations should be declared. For primary outcome, fusion was varied by studies. Some studies used radiography, while others used dynamic view or CT to determine solid fusion. The finding of fusion rate might be not seriously affected by the definition, and heterogeneity of the pooled estimate is low ( $I^2 = 0\%$ ) even though the tools for solid fusion are different in the included RCTs. For most secondary outcomes, the network analysis could not form a loop and decreased the reliability of the result. Most of the studies only reported short-term or mid-term results, and there are no data about complication after 5-year follow-up. In the future, high-quality RCTs with longer follow-up are still necessary. Besides, evidence on some clinical outcomes were insufficient, including operative time, hospital stay, and cost. These outcomes may also associate to lumbar fusion procedures since the techniques this study discussed can be done in one day or staged. Consequently, the clinical outcomes raise concerns in clinical practice. These ultimate outcome measures ought to be further assessed by studies in the future.

### Conclusions

Collectively, the present evidence indicated that circumferential fusion might be worth to be recommended for lumbar spondylolisthesis management because it exhibits the best balance between fusion rate and overall adverse event. PLF is still an inferior procedure and requires shorter operative time than other procedures. To improve clinical practice, operative time, hospital stay, and cost should be evaluated in the future.

### Authors' Note

Conceptualization: Shih-Hao Cheng and Yi-No Kang; Data curation: Shih-Hao Cheng; Formal analysis: Yi-No Kang; Interpretation: Yi-No Kang, Yu-Wan Ho, Shih-Hao Cheng; Investigation: Yi-No Kang, Yu-Wan Ho, Shih-Hao Cheng; Methodology: Yi-No Kang; Supervision: Yu-Wan Ho, William Chu, Wen-Shiang Chou; Visualization: Yi-No Kang; Writing – original draft: Yi-No Kang, Shih-Hao Cheng; Writing – review & editing: Yu-Wan Ho, William Chu, Wen-Shiang Chou.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.



## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## ORCID iD

Shih-Hao Cheng, MD  <https://orcid.org/0000-0001-8579-8792>

## Supplemental Material

Supplemental material for this article is available online.

## References

- Ganju A. Isthmic spondylolisthesis. *Neurosurg Focus*. 2002;13(1):E1.
- Jacobsen S, Sonne-Holm S, Røvsing H, Monrad H, Gebuhr P. Degenerative lumbar spondylolisthesis: an epidemiological perspective: the Copenhagen Osteoarthritis Study. *Spine*. 2007;32(1):120-125.
- Kreiner DS, Baisden J, Mazanec DJ, et al. Guideline summary review: an evidence-based clinical guideline for the diagnosis and treatment of adult isthmic spondylolisthesis. *Spine J*. 2016;16(12):1478-1485.
- Jones TR, Rao RD. Adult isthmic spondylolisthesis. *J Am Acad Orthop Surg*. 2009;17(10):609-617.
- Kalichman L, Kim DH, Li L, Guermazi A, Berkin V, Hunter DJ. Spondylolysis and spondylolisthesis: prevalence and association with low back pain in the adult community-based population. *Spine*. 2009;34(2):199-205.
- Kalichman L, Hunter DJ. Diagnosis and conservative management of degenerative lumbar spondylolisthesis. *Eur Spine J*. 2008;17(3):327-335.
- Weinstein JN, Lurie JD, Tosteson TD, et al. Surgical versus non-surgical treatment for lumbar degenerative spondylolisthesis. *N Engl J Med*. 2007;356(22):2257-2270.
- Møller H, Hedlund R. Surgery versus conservative management in adult isthmic spondylolisthesis—a prospective randomized study: part 1. *Spine*. 2000;25(13):1711-1715.
- Jacobs WC, Vreeling A, De Kleuver M. Fusion for low-grade adult isthmic spondylolisthesis: a systematic review of the literature. *Spine J*. 2006;15(4):391-402.
- Kwon BK, Hilibrand AS, Malloy K, et al. A critical analysis of the literature regarding surgical approach and outcome for adult low-grade isthmic spondylolisthesis. *J Spinal Disord Tech*. 2005;18(suppl):S30-S40.
- Cole CD, McCall TD, Schmidt MH, Dailey AT. Comparison of low back fusion techniques: transforaminal lumbar interbody fusion (TLIF) or posterior lumbar interbody fusion (PLIF) approaches. *Curr Rev Musculoskelet Med*. 2009;2(2):118-126.
- Gottschalk MB, Premkumar A, Sweeney K, et al. Posterolateral lumbar arthrodesis with and without interbody arthrodesis for L4-L5 degenerative spondylolisthesis: a comparative value analysis. *Spine*. 2015;40(12):917-925.
- Min JH, Jang JS, Lee SH. Comparison of anterior- and posterior-approach instrumented lumbar interbody fusion for spondylolisthesis. *J Neurosurg Spine*. 2007;7(1):21-26.
- Barbanti Brodano G, Gasbarrini A, Bandiera S, et al. Comparison between posterior interbody fusion (PLIF) and transforaminal interbody fusion (TLIF) in the treatment of degenerative and isthmic spondylolisthesis. *Eur Spine J*. 2012;21(4):784.
- Ekman P, Møller H, Tullberg T, Neumann P, Hedlund R. Posterior lumbar interbody fusion versus posterolateral fusion in adult isthmic spondylolisthesis. *Spine*. 2007;32(20):2178-2183.
- Parker SL, Mendenhall SK, Shau DN, et al. Minimally invasive versus open transforaminal lumbar interbody fusion for degenerative spondylolisthesis: comparative effectiveness and cost-utility analysis. *World Neurosurg*. 2014;82(1-2):230-238.
- Parker SL, Mendenhall SK, Shau DN, et al. Minimally invasive versus open Transforaminal Lumbar Interbody Fusion (TLIF) for degenerative spondylolisthesis: comparative effectiveness and cost-utility analysis. *Spine J*. 2012;22(9):45S.
- Mukai Y, Takenaka S, Hosono N, Miwa T, Fuji T. Intramuscular pressure of the multifidus muscle and low-back pain after posterior lumbar interbody fusion: comparison of mini-open and conventional approaches. *J Neurosurg Spine*. 2013;19(6):651-657.
- Phan K, Maharaj M, Assem Y, Mobbs RJ. Review of early clinical results and complications associated with oblique lumbar interbody fusion (OLIF). *J Clin Neurosci*. 2016;31:23-29.
- Abdelkader SG, El Zahawy HN, Elkhateeb TM. Interbody fusion versus posterolateral fusion in treatment of low grade lytic spondylolisthesis. *Acta Orthop Belg*. 2019;85(3):269-273.
- Alijani B, Emamhadi M, Behzadnia H, et al. Posterior lumbar interbody fusion and posterolateral fusion: analogous procedures in decreasing the index of disability in patients with spondylolisthesis. *Asian J Neurosurg*. 2015;10(1):51.
- Challier V, Boissiere L, Obeid I, et al. One-level lumbar degenerative spondylolisthesis and posterior approach: is transforaminal lateral interbody fusion mandatory?: A randomized controlled trial with 2-year follow-up. *Spine*. 2017;42(8):531-539.
- Cheng L, Nie L, Zhang L. Posterior lumbar interbody fusion versus posterolateral fusion in spondylolisthesis: a prospective controlled study in the Han nationality. *Int Orthop*. 2009;33(4):1043-1047.
- Etemadifar MR, Hadi A, Masouleh MF. Posterolateral instrumented fusion with and without transforaminal lumbar interbody fusion for the treatment of adult isthmic spondylolisthesis: a randomized clinical trial with 2-year follow-up. *J Craniovertebr Junction Spine*. 2016;7(1):43-49.
- Fariborz S, Gharedaghi M, Khosravi AF, Samini M. Comparison of results of 4 methods of surgery in grade 1 lumbosacral spondylolisthesis. *Neurosurgery*. 2016;26(1):14-18.
- Farrokhi MR, Rahmani A, Masoudi MS. Posterolateral versus posterior interbody fusion in isthmic spondylolisthesis. *J Neurotrauma*. 2012;29(8):1567-1573.
- Fei Q, Wang YP, Xu HG, et al. Comparison of instrumented posterior fusion with instrumented circumferential lumbar fusion in the treatment of lumbar stenosis with low degree lumbar spondylolisthesis. *Zhonghua wai ke za*. 2005;43(8):486-490.
- Inamdar DN, Alagappan M, Shyam L, Devadoss S, Devadoss A. Posterior lumbar interbody fusion versus intertransverse fusion in the treatment of lumbar spondylolisthesis. *J Orthop Surg (Hong Kong)*. 2006;14(1):21-26.
- Isaacs RE, Sembrano JN, Tohmeh AG. Two-year comparative outcomes of MIS lateral and MIS transforaminal interbody fusion

- in the treatment of degenerative spondylolisthesis: part II: radiographic findings. *Spine*. 2016;41(suppl 8):S133-144.
30. Lee GW, Lee SM, Ahn MW, Kim HJ, Yeom JS. Comparison of posterolateral lumbar fusion and posterior lumbar interbody fusion for patients younger than 60 years with isthmic spondylolisthesis. *Spine*. 2014;39(24):E1475-1480.
  31. Musluman AM, Yilmaz A, Cansever T, et al. Posterior lumbar interbody fusion versus posterolateral fusion with instrumentation in the treatment of low-grade isthmic spondylolisthesis: midterm clinical outcomes. *J Neurosurg Spine*. 2011;14(4):488-496.
  32. Sembrano JN, Tohmeh A, Isaacs R. Two-year comparative outcomes of MIS lateral and MIS transforaminal interbody fusion in the treatment of degenerative spondylolisthesis. *Spine*. 2016;41:s123-s132.
  33. Serban D, Calina N, Tender G. Standard versus minimally invasive transforaminal lumbar interbody fusion: a prospective randomized study. *Biomed Res Int*. 2017;2017:7236970.
  34. Yang EZ, Xu JG, Liu XK, et al. An RCT study comparing the clinical and radiological outcomes with the use of PLIF or TLIF after instrumented reduction in adult isthmic spondylolisthesis. *Eur Spine J*. 2016;25(5):1587-1594.
  35. Ulmer JL, Elster AD, Mathews VP, King JC. Distinction between degenerative and isthmic spondylolisthesis on sagittal MR images: importance of increased anteroposterior diameter of the spinal canal ("wide canal sign"). *AJR Am J Roentgenol*. 1994;163(2):411-416.
  36. Ntoukas V, Muller A. Minimally invasive approach versus traditional open approach for one level posterior lumbar interbody fusion. *Minim Invasive Neurosurg*. 2010;53(1):21-24.
  37. DePalma AF, Rothman RH. The nature of pseudarthrosis. *Clin Orthop Relat Res*. 1968;59:113-118.
  38. Kornblum MB, Fischgrund JS, Herkowitz HN, Abraham DA, Berkower DL, Ditkoff JS. Degenerative lumbar spondylolisthesis with spinal stenosis: a prospective long-term study comparing fusion and pseudarthrosis. *Spine*. 2004;29(7):726-733. Discussion 733-724.
  39. Zdeblick TA. A prospective, randomized study of lumbar fusion. Preliminary results. *Spine*. 1993;18(8):983-991.
  40. Carpenter CT, Dietz JW, Leung KY, Hanscom DA, Wagner TA. Repair of a pseudarthrosis of the lumbar spine. A functional outcome study. *J Bone Joint Surg Am*. 1996;78(5):712-720.
  41. Herkowitz HN, Kurz LT. Degenerative lumbar spondylolisthesis with spinal stenosis. A prospective study comparing decompression with decompression and intertransverse process arthrodesis. *J Bone Joint Surg Am*. 1991;73(6):802-808.
  42. Booth KC, Bridwell KH, Eisenberg BA, Baldus CR, Lenke LG. Minimum 5-year results of degenerative spondylolisthesis treated with decompression and instrumented posterior fusion. *Spine*. 1999;24(16):1721-1727.
  43. Wu RH, Fraser JF, Hartl R. Minimal access versus open transforaminal lumbar interbody fusion: meta-analysis of fusion rates. *Spine*. 2010;35(26):2273-2281.
  44. Khan NR, Clark AJ, Lee SL, Venable GT, Rossi NB, Foley KT. Surgical outcomes for minimally invasive vs open transforaminal lumbar interbody fusion: an updated systematic review and meta-analysis. *Neurosurgery*. 2015;77(6):847-874. discussion 874.
  45. Ye YP, Xu H, Chen D. Comparison between posterior lumbar interbody fusion and posterolateral fusion with transpedicular screw fixation for isthmic spondylolithesis: a meta-analysis. *Arch Orthop Trauma Surg*. 2013;133(12):1649-1655.
  46. Cho JY, Goh TS, Son SM, Kim DS, Lee JS. Comparison of anterior approach and posterior approach to instrumented interbody fusion for spondylolisthesis: a meta-analysis. *World Neurosurg*. 2019;129:e286-e293.
  47. Liu X, Wang Y, Qiu G, Weng X, Yu B. A systematic review with meta-analysis of posterior interbody fusion versus posterolateral fusion in lumbar spondylolisthesis. *Spine J*. 2014;23(1):43-56.
  48. Champagne PO, Walsh C, Diabira J, et al. Sagittal balance correction following lumbar interbody fusion: a comparison of the three approaches. *Asian Spine J*. 2019;13(3):450-458.
  49. Lin GX, Akbary K, Kotheeranurak V, et al. Clinical and radiologic outcomes of direct versus indirect decompression with lumbar interbody fusion: a matched-pair comparison analysis. *World Neurosurg*. 2018;119:E898-E909.
  50. Chandra V, Singh RK. Anterior lumbar inter-body fusion with instrumentation compared with posterolateral fusion for low grade isthmic-spondylolisthesis. *Acta Orthop Belg*. 2016;82(1):23-30.