



Systematic review and meta-analysis of the therapeutic effects of minimally invasive transforaminal interbody fusion on spondylolisthesis

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Background: Minimally invasive transforaminal interbody fusion (MI-TLIF) can minimize surgical incision, tissue damage, and intraoperative blood loss in the treatment of spondylolisthesis. However, there is a lack of evidence-based research to confirm its clinical efficacy.

Methods: Chinese and English databases were searched with “open”, “minimally invasive transforaminal interbody fusion”, “MIS-TLIF”, “spondylolisthesis”, and “open transforaminal interbody fusion” as search terms. Rev Man 5.3 provided by the Cochrane system was used to assess the quality of the literature.

Results: Of the 12 randomized controlled trials (RCTs), 7 references were level A (58.34%), 4 were B level (33.33%), and 1 reference was C level (8.33%). There was a statistically significant difference in intraoperative blood loss between MI-TLIF and open transforaminal interbody fusion (O-TLIF) in the treatment of spondylolisthesis [mean difference (MD) = -349.35, 95% confidence interval (CI): (-410.66, -288.03), $P < 0.00001$]. There was also a statistically significant difference in visual analogue scale (VAS) scores before and after MI-TLIF at the last follow-up [MD = 5.72, 95% CI: (4.83, 6.62), $P < 0.00001$], and in the complication rate between MI-TLIF and O-TLIF [odds ratio (OR) = 0.48, 95% CI: (0.30, 0.76), $P < 0.00001$].

Discussion: This meta-analysis confirmed that MI-TLIF could significantly reduce intraoperative blood loss, mitigate patient pain, and reduce the incidence of complications without increasing the operation time in the treatment of spondylolisthesis.

Keywords: Minimally invasive transforaminal interbody fusion (MI-TLIF); orthopedics; spondylolisthesis

Submitted Jul 20, 2021. Accepted for publication Sep 02, 2021.

doi: 10.21037/apm-21-2137

View this article at: <https://dx.doi.org/10.21037/apm-21-2137>

Introduction

Spondylolisthesis is a degenerative disease of the spine arising from abnormal connection between adjacent vertebral bodies so that the upper vertebral body is partially or completely slipped relative to the lower vertebral body. It is common in middle-aged and elderly people (1).

At present, there are mainly two types of transforaminal interbody fusion (TLIF). One is open transforaminal interbody fusion (O-TLIF), and the other is minimally invasive transforaminal interbody fusion (MI-TLIF) (2). Of the two, O-TLIF has been used extensively and is favored by scholars because it involves less surgical trauma, less

blood loss, and faster recovery time. However, it is likely to cause problems such as a loss of intervertebral motion and accelerated adjacent vertebrae degeneration (3). MI-TLIF was first proposed by Foley in 2002 (4), and during this minimally invasive procedure, a damaged disc in the lumbar spine is replaced with an expandable implant, and hardware to stabilize the spine. This procedure relieves nerve root compression, which is a common cause of pain in back and legs (5). The surgeon inserts a needle into the back, and carefully passes it through a natural opening in the spine called a foramen, reducing tissue damage and preserving bone. The needle is pushed into the target disc, a guide wire is passed through the needle, and the needle is removed. The guide wire is used to direct a dilator, and then a metal tube into the disc, creating a larger opening for implanting (6). At present, the technique of spinal fusion is recognized as the “gold standard” for the treatment of spondylolisthesis (7).

The short-term efficacy of MI-TLIF in the treatment of spondylolisthesis was analyzed. It did not require dissection of the paraspinal muscle and caused little muscle damage. The postoperative pain experience of patients was relatively mild and the functional exercise time was advanced, which was conducive to rapid recovery. However, the long-term efficacy of MI-TLIF is still controversial. Lau *et al.* [2013] (8) showed that there was no significant difference between the long-term effect of mi-TLIF and posterior interbody fusion. Patients can benefit from MI-TLIF in many ways. A minimally invasive approach reduces time in the operating room and minimizes blood loss and tissue damage. It helps minimize pain during healing and also speeds recovery time and reduces the chance for complications. However, the efficacy of MI-TLIF and O-TLIF has not been analyzed systematically.

Existing research is mostly single-center randomized controlled trials (RCTs) with small sample sizes. In this study, a meta-analysis was conducted to compare the efficacy of MI-TLIF and O-TLIF, to provide a scientific evidence-based platform for the clinical treatment of spondylolisthesis.

We present the following article in accordance with the PRISMA reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-2137>).

Methods

Literature retrieve

With “open”, “minimally invasive transforaminal interbody

fusion”, “MIS-TLIF”, “spondylolisthesis”, and “open transforaminal interbody fusion” as search subjects, Chinese and English databases were searched from the establishment of the database to March 15th, 2021 for RCTs on MI-TLIF in the treatment of spondylolisthesis databases included PubMed, Medline, Embase, Web of Sciences, Chinese Biomedical Literature, Wanfang Chinese Biomedical Association Digital Journals, Wanfang Digital Journals Full-Text Database, and Weipu Chinese Sci-Tech Journals Full-Text Database.

The Boolean logic retrieval method was used to retrieve relevant references, and Rev Man 5.3 provided by the Cochrane system was used to evaluate the quality of the literature.

Some references were initially eliminated after reading the titles and abstracts, then a second screening was performed according to the inclusion criteria and exclusion criteria, and the reference was traced using a search engine. Finally, a third screening was conducted by reading the full text of the included literature.

Inclusion and exclusion criteria

References were selected as per the following inclusion criteria: (I) RCTs and retrospective case-control studies; (II) the subjects were spondylolisthesis patients for whom conservative treatment was ineffective for at least 5 weeks; (III) in the pathological control analysis, the index was reliable in the 95% confidence interval (CI); (IV) surgical methods were MI-TLIF and O-TLIF; (V) the study contained complete clinical basics data and observation indicators.

Exclusion criteria: (I) the patient had other systemic diseases; (II) the patient had received other types of surgery at the surgical site; (III) repeated published studies; (IV) related conference speeches, literature reviews, case study reports, lectures, and commentary literature; (V) studies with incomplete data.

Two senior experts performed the literature screening, and any inconsistency was resolved by discussion or inviting another expert to arbitrate.

Observation indicators

These were operation time, postoperative drainage volume, radiation exposure time, visual analogue scale (VAS) at the last follow-up, fusion rate at the last follow-up, and incidence of complications.

Table 1 Newcastle-Ottawa Scale (NOS)

Items	Evaluation results
Is the case diagnosed appropriately?	Yes, the case is correctly diagnosed. (At least two doctors diagnose the patient independently) Yes, the patient is diagnosed based on medical records or the doctor's own records, but there are no original records No description
Case representation	Representative cases (cases with the target disease within a specified time; all cases in a specific hospital or clinic; a random sample obtained from these cases) There is potential selection bias or no description
Control selection	Community control Hospital control No description
Definition of control	No history of disease (no end-point event) No description

Data extraction

Two experts used unified Microsoft Excel to independently collate data and any inconsistency was resolved by discussion or inviting another expert to arbitrate. The following data were collated: (I) research title, research time, research type, follow-up time, and number of cases lost to follow-up; (II) first author's name, publication year, and publication name; (III) general information of the research object, including region, sample size, gender ratio, and age distribution; (IV) observation indicators, including operation time, postoperative drainage volume, and radiation exposure time.

Risk of bias and quality assessment

Two researchers conducted a risk assessment of bias simultaneously. Any inconsistencies were resolved via discussion or arbitration by a third expert. In this study, the Cochrane Collaboration for "bias risk assessment" was used for RCTs. The assessments of "low risk bias", "unclear", and "high risk bias" were made according to the four aspects of random method, blind method, allocation concealment, and the number of cases lost to follow up.

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the literature according to four aspects, namely, patient selection, comparability of the study, exposure assessment, and outcome. Each item accounted for 1 point, and the total score ranged from 0–9 points. A score of 6–9 points was considered A-level research (low risk), 3–5

points were considered B-level research (unclear risk), and 0–2 was considered C-level research (high risk) (Table 1).

Statistics

Stata SE12.0 (College Station, USA) was used for statistical analysis and Rev Man 5.3 was used to assess the risk bias of the included references. Each effect was represented by a 95% CI. When $P > 0.01$ and $I^2 < 50\%$, the fixed effects model (FEM) was used for meta-analysis, and when $P < 0.01$ and $I^2 > 50\%$, the random effects model (REM) was used.

Results

Basic information of the included references

In total, 126 articles were obtained from the database and 139 articles were obtained from the register in this paper. By reading the abstract and title of the articles, 29 articles were repeatedly published, 43 articles were unqualified, and 32 articles were for other reasons, leaving 161 articles. After reading the full text, 63 articles with repeated subjects were eliminated, leaving 98 articles. 51 review reports were excluded, leaving 47. The 35 articles that could not be extracted were excluded, and 12 articles were finally included in the study. Figure 1 shows the quality evaluation results of the NOS. It was noted that, 7 references (58.33%) scored 6–9, 3 (25%) scored 3–5, and 2 (16.67%) scored 0–2 (Figure 2).

A total of 842 cases were involved in the 12 references.

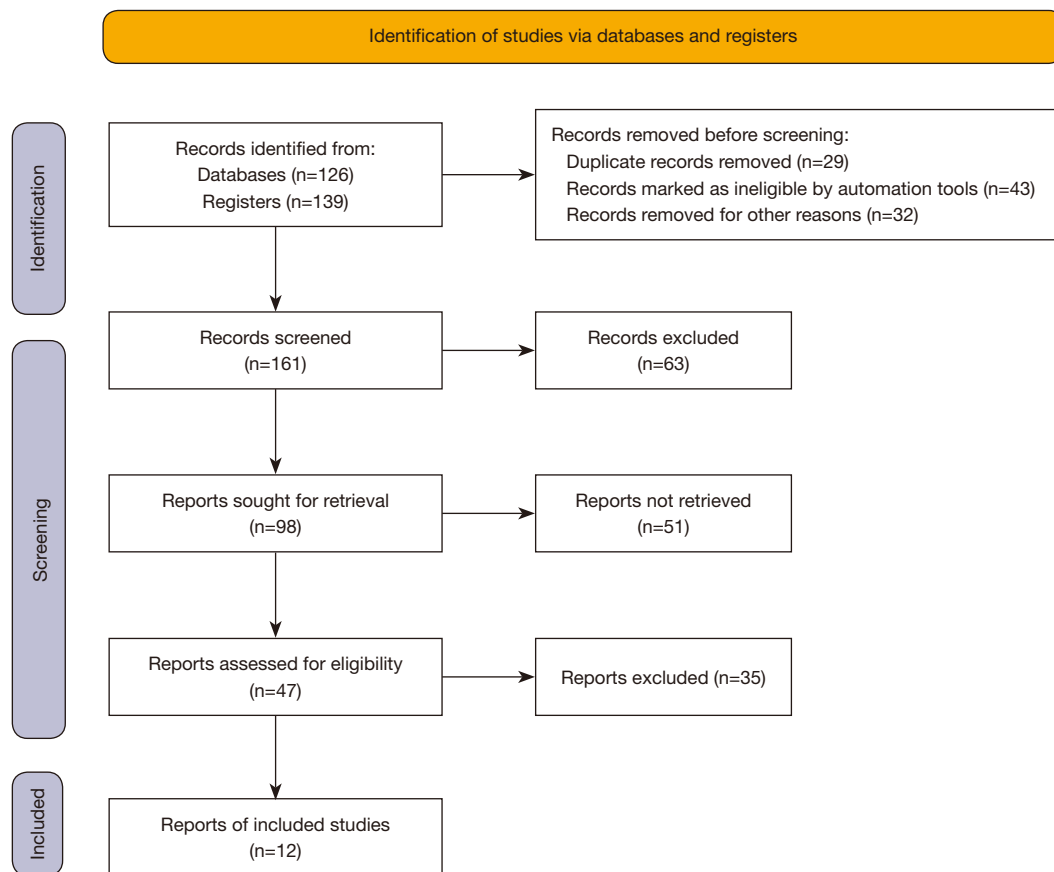


Figure 1 Flow chart showing the retrieval process.

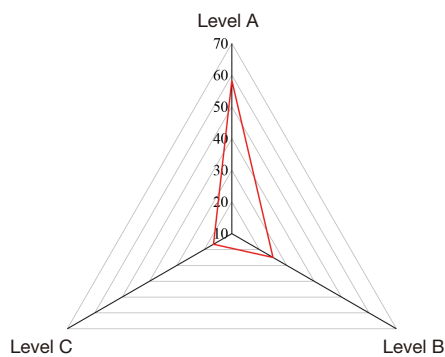


Figure 2 NOS results. NOS, Newcastle-Ottawa Scale.

All were small-sample studies, with the sample size ranging from 49 to 102 cases, and all research subjects were over 20 years old. All 12 references described the sample size, gender ratio, age, operation time, postoperative drainage volume, radiation exposure time, Oswestry disability index (ODI) score, VAS at the last follow-up, fusion rate at the

last follow-up, and incidence of complications. *Table 2* shows the basic characteristics of the included literature.

Risk bias assessment

Figures 3,4 show the multiple risk bias results of the included references assessed by Rev Man 5.3. Of the 12 RCTs in this study, four (9-12) described the correct random allocation method, accounting for 33.33%, and two (13,14) described the concealment allocation in detail, accounting for 16.67%. Of the 12 RCTs, only one (15) of 12 used the blind method, accounting for 8.33%.

Operation time

Figure 5 is a forest plot of the operation time. Of the 12 RCTs, eight described the mean difference (MD) and standard deviation (SD) of the operation time in detail, and the heterogeneity results showed that $I^2=0\%<50\%$,

Table 2 Basic characteristics of included literature

Author	Year of publication	Sample size (example)	Gender (male/female)	Age (year)	Outcome indicators
Mobbs RJ	2015	55	28/27	31.26±12.34	Surgical incision length, blood loss, visual analogue scale (VAS) at the last follow-up, fusion rate at the last follow-up, and complication rate
Ahn Y	2019	49	25/24	43.26±13.67	Operation time, blood loss, radiation exposure time, VAS at the last follow-up, complication rate
Badlani N	2020	65	35/30	25.45±15.49	Operation time, blood loss, radiation exposure time, VAS at the last follow-up, fusion rate at the last follow-up, and complication rate
Serban D	2017	75	36/39	34.67±17.52	Operation time, blood loss, radiation exposure time, VAS at the last follow-up, Japanese Orthopaedic Association (JOA) score, complication rate
Hari A	2016	87	41/46	42.58±16.54	VAS at the last follow-up, blood loss, fusion rate at the last follow-up, complication rate, radiological indicators
Chandra Vemula VR	2018	95	48/47	26.69±8.52	Bleeding volume, operation time, VAS at the last follow-up, fusion rate at the last follow-up, and complication rate
Lau D	2013	102	52/50	45.67±17.52	Radiation exposure time, EuroQol five-dimensional (EQ-5D) score, VAS at the last follow-up, complication rate
Tsahtsarlis A	2012	71	35/36	44.52±13.54	Operation time, blood loss, radiation exposure time, VAS at the last follow-up, complication rate, medical expenses
Holly LT	2006	69	34/35	35.69±13.84	Operation time, blood loss, radiation exposure time, VAS at the last follow-up, and fusion rate at the last follow-up
Park Y	2011	54	25/29	36.52±12.64	Operation time, blood loss, hospital stay, radiation exposure time, VAS at the last follow-up, fusion rate at the last follow-up, and complication rate
Isaacs RE	2005	49	26/23	55.36±13.21	Operation time, hospital stay, blood loss, radiation exposure time, complication rate
Wang J	2010	71	32/39	45.62±12.25	Operation time, blood loss, radiation exposure time, VAS at the last follow-up

$P=0.70$, indicating that there was no heterogeneity. REM was then used for analysis, which showed there was no significant difference in the operation time between MI-TLIF and O-TLIF for spondylolisthesis [MD = -19.99, 95% CI: (-23.95, -16.04), $P<0.00001$], indicating there was no significant difference in the operation time for the two methods.

Intraoperative blood loss

Figure 6 shows the meta-analysis results of intraoperative blood loss. Of the 12 RCTs, 11 described the MD and SD of intraoperative blood loss in detail, while heterogeneity results showed that $I^2=93\%>50\%$, $P<0.00001$, indicating

obvious heterogeneity. RCT was then used for analysis and showed the difference in intraoperative blood loss between MI-TLIF and O-TLIF was statistically significant [MD = -349.35, 95% CI: (-410.66, -288.03), $P<0.00001$]. Compared with O-TLIF, MI-TLIF could reduce intraoperative blood loss.

Intraoperative radiation exposure time

Figure 7 shows the meta-analysis results of intraoperative radiation exposure time, and of the 12 RCTs, nine described the MD and SD in detail. The heterogeneity results showed that $I^2=94\%>50\%$, $P<0.00001$, indicating obvious heterogeneity. REM was then used and showed

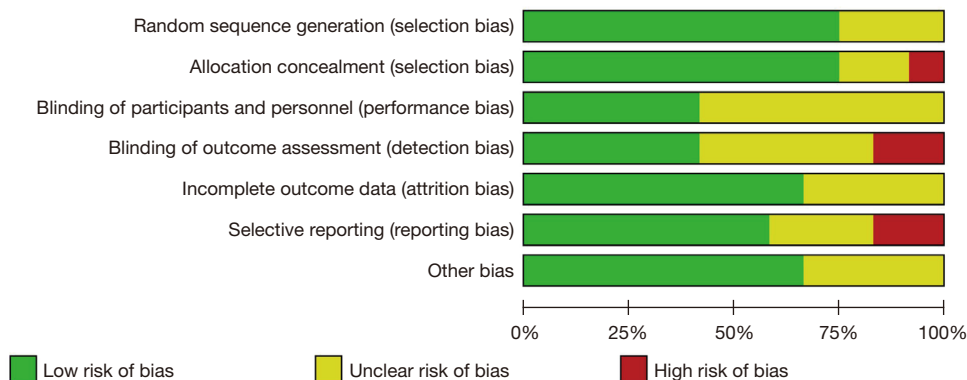


Figure 3 Risk bias assessment.

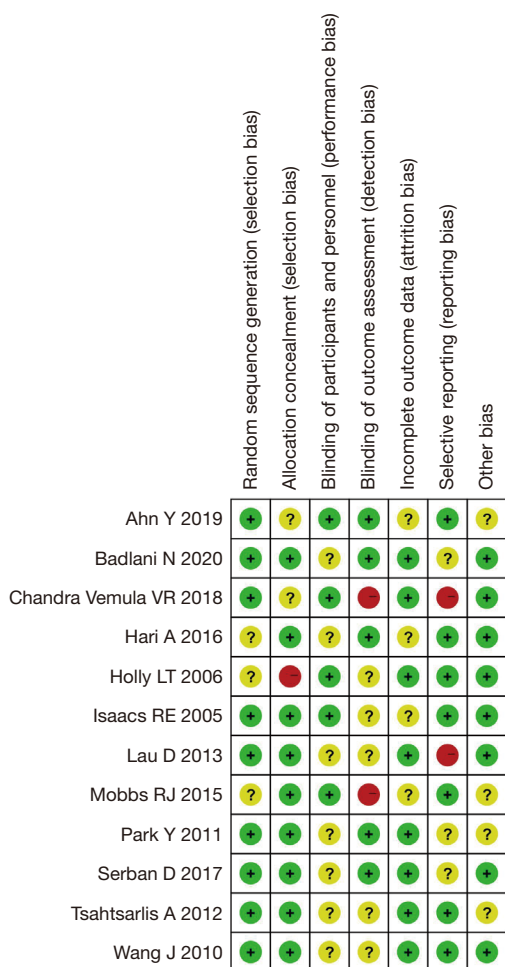


Figure 4 Multiple risk bias assessment. + = low risk bias; - = high risk bias; ? = unclear.

the difference in intraoperative radiation exposure time between MI-TLIF and O-TLIF was statistically significant [MD =35.72, 95% CI: (28.11, 43.33), P<0.00001], with MI-TLIF’s radiation exposure time significantly reduced in comparison to OTLIF.

Fusion rate at the last follow-up

Figure 8 shows the meta-analysis results of the fusion rate at the last follow-up, and of the 12 RCTs, six described the mean and SD in detail. The heterogeneity results showed that I²=0%<50%, P=0.99, indicating there was no heterogeneity. FEM was then used for analysis and showed the fusion rate of MI-TLIF and O-TLIF was not statistically significant [odds ratio (OR) =0.80, 95% CI: (0.31, 2.06), P=0.64], indicating the two treatment methods had similar fusion rates.

VAS score

Figures 9,10 show the meta-analysis results of VAS scores, and of the 12 RCTs, seven described the MD and SD of pain improvement in detail. The heterogeneity results of the VAS score showed that I²=96%>50%, P<0.00001, indicating obvious heterogeneity. REM was then used for analysis, and showed a statistically significant difference in VAS scores before and after O-TLIF at the last follow-up [MD =6.04, 95% CI: (4.94, 7.14), P<0.00001], and in VAS scores before and after MI-TLIF at the last follow-up [MD =5.72, 95% CI: (4.83, 6.62), P<0.00001].

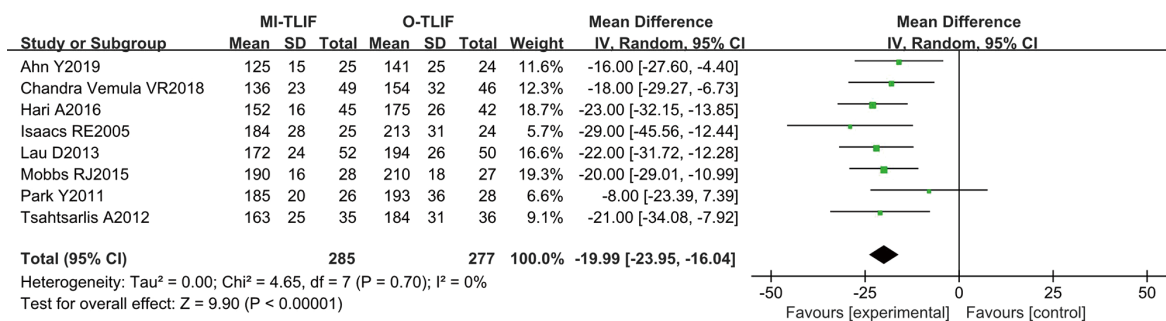


Figure 5 Forest plot of operation time. MI-TLIF, minimally invasive transforaminal interbody fusion; O-TLIF, open transforaminal interbody fusion; SD, standard deviation; CI, confidence interval.

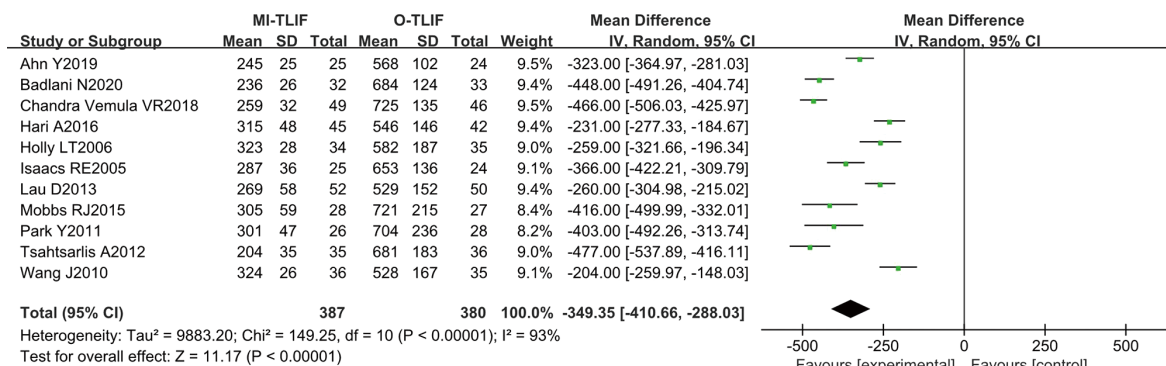


Figure 6 Meta-analysis results of intraoperative blood loss. MI-TLIF, minimally invasive transforaminal interbody fusion; O-TLIF, open transforaminal interbody fusion; SD, standard deviation; CI, confidence interval.

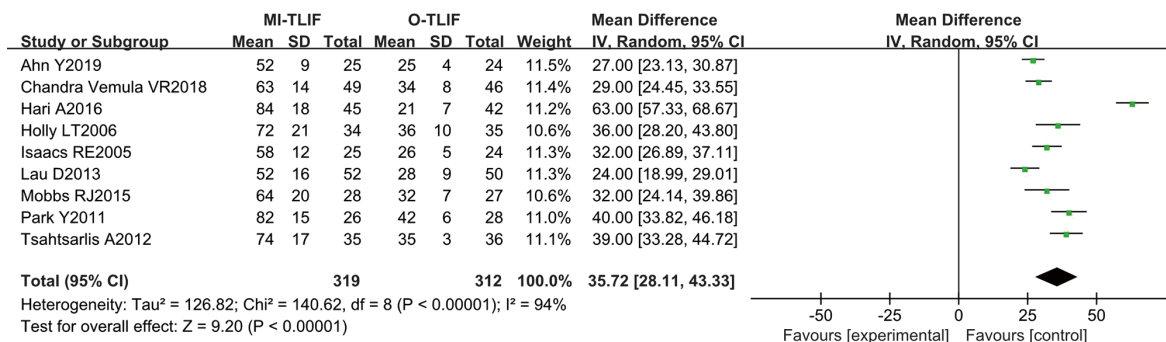


Figure 7 Meta-analysis results of intraoperative radiation exposure time. MI-TLIF, minimally invasive transforaminal interbody fusion; O-TLIF, open transforaminal interbody fusion; SD, standard deviation; CI, confidence interval.

Complication rate

Figure 11 shows the meta-analysis results of the incidence of complications, and of the 12 RCTs, 10 described the MD and SD of the complication rate in detail. The heterogeneity

results showed that I²=0%<50%, P=0.58, indicating no heterogeneity. FEM was then used for analysis, and showed the complication rate difference between MI-TLIF and O-TLIF treatment was statistically significant [OR =0.48, 95% CI: (0.30, 0.76), P=0.002] Compared to O-TLIF, MI-

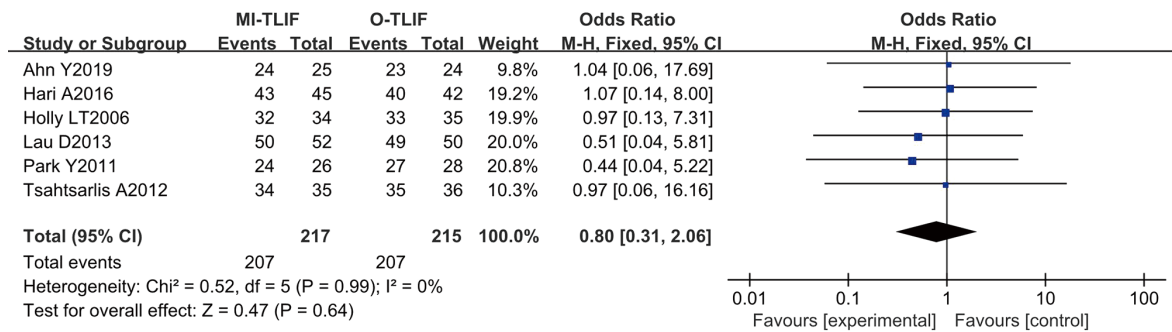


Figure 8 Meta-analysis results of the fusion rate at the last follow-up. MI-TLIF, minimally invasive transforaminal interbody fusion; O-TLIF, open transforaminal interbody fusion; CI, confidence interval.

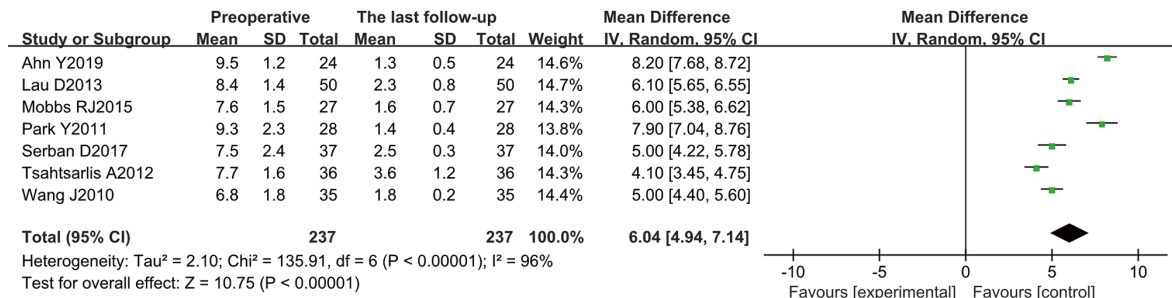


Figure 9 Meta-analysis results of VAS scores before and after O-TLIF at the last follow-up. VAS, visual analogue scale; O-TLIF, open transforaminal interbody fusion; SD, standard deviation; CI, confidence interval.

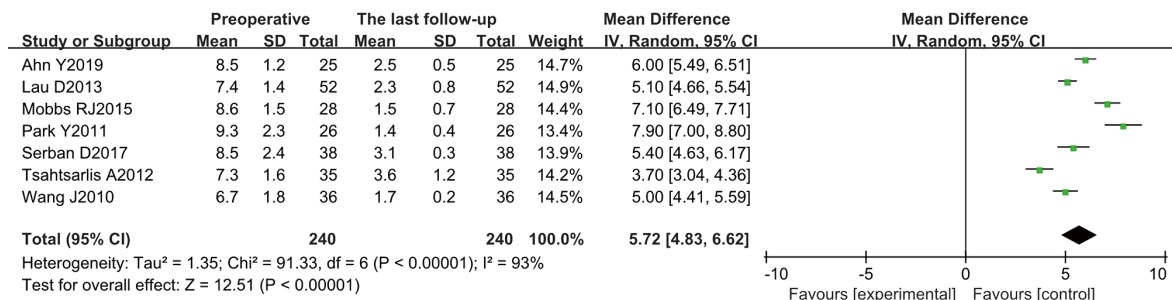


Figure 10 Meta-analysis results of visual pain scores before and after MI-TLIF at the last follow-up. MI-TLIF, minimally invasive transforaminal interbody fusion; SD, standard deviation; CI, confidence interval.

TLIF could reduce the incidence of complications.

no bias in publications, and the conclusions obtained were credible.

Publication of bias

Figure 12 is a funnel chart of the publication bias of the included literature. This shows the circles in some studies were basically symmetrical along the center line, there was

Discussion

Spondylolisthesis is a common spinal disease, and foraminal interbody fusion is a standard treatment

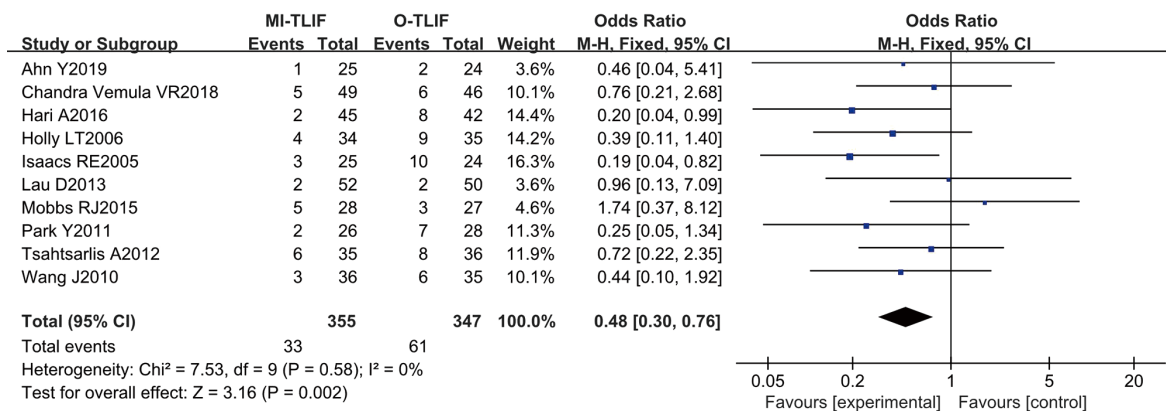


Figure 11 Meta-analysis results of complication rate. MI-TLIF, minimally invasive transforaminal interbody fusion; O-TLIF, open transforaminal interbody fusion; CI, confidence interval.

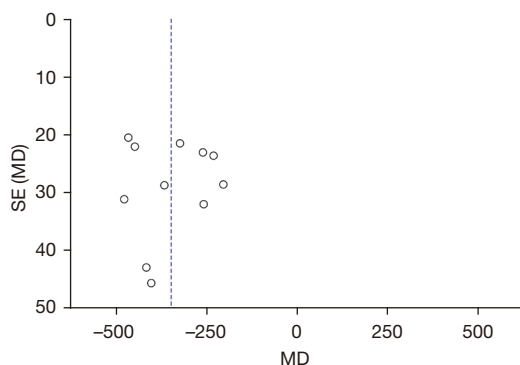


Figure 12 Funnel chart of the publication bias of the included literature. This indicated the included literature was reliable, and risk bias was not a key factor affecting the conclusion. SE, standard error; MD, mean difference.

method (16). Clinically, TLIF has been widely used for the treatment of degenerative diseases of the lumbar spine, and compared with posterior interbody fusion, can reduce the risk of nerve injury and maintain the stability of the posterior column (17). MI-TLIF is used to treat degenerative spondylolisthesis and spondylolisthesis. For spondylolisthesis, the bone in the spondylolisthesis is damaged, and postoperative treatment such as reduction, bone grafting, fusion, and repair is needed, resulting in more blood loss and longer operation time in spondylolisthesis than in degenerative spondylolisthesis. However, traditional intervertebral transforaminal fusion may lead to multifidus muscle dissection and muscle nerve atrophy, while MI-TLIF results in less damage to the

paraspinal muscle, reduces avascular necrosis and aseptic inflammation, and maintains the stability of the spine. MI-TLIF is a new interbody fusion technology developed in the past decade. Compared with traditional open surgery, MI-TLIF has the advantage of avoiding a wide range of muscle and soft tissue dissection or cutting, significantly reducing intraoperative bleeding, postoperative pain, and hospital stay, and reducing nerve root stimulation and postoperative scar formation. Because of adequate bone contact surface and abundant blood supply, intervertebral bone grafting can achieve satisfactory fusion rates.

A minimally invasive approach reduces time in the operating room, minimizes blood loss and tissue damage, and helps minimize pain during healing. It also speeds recovery time and reduces the chance of complications (18). While there was no significant difference in operation time between MI-TLIF and O-TLIF for spondylolisthesis [MD = -19.99, 95% CI: (-23.95, -16.04), P<0.00001], there was in intraoperative blood loss [MD = -349.35, 95% CI: (-410.66, -288.03), P<0.00001]. This suggests the operation time of the two surgical treatments was not significantly different, but MI-TLIF could significantly reduce the amount of intraoperative blood loss, which was consistent with the results of Kirnaz *et al.* [2020] (19). This may be associated with the small surgical incisions used in MI-TLIF and low tissue damage.

There was a statistically significant difference in the VAS before and after O-TLIF [MD = 6.04, 95% CI: (4.94, 7.14), P<0.00001] and after MI-TLIF [MD = 5.72, 95% CI: (4.83, 6.62), P<0.00001] at the last follow-up. This showed that both treatment methods could significantly improve the

pain of patients. The complication rate difference between MI-TLIF and O-TLIF was also statistically significant [OR =0.48, 95% CI: (0.30, 0.76), P=0.002], and compared with O-TLIF, MI-TLIF could reduce the incidence of complications. The occurrence of complications may be related to factors such as the technological difficulties of minimally invasive surgery and the long learning curve (20,21).

A meta-analysis was conducted on MI-TLIF in the treatment of spondylolisthesis, and a funnel chart was drawn. This showed there was no bias in publication, and the conclusions obtained were credible, and risk bias was not the main factor affecting the conclusion.

Conclusions

In this meta-analysis, the compound logic search method was used to retrieve 12 RCTs on MI-TLIF in the treatment of spondylolisthesis. It was confirmed that MI-TLIF can significantly reduce intraoperative blood loss, mitigate patient pain, and reduce the incidence of complications without increasing the operation time. A limitation of this study is that the number of studies on MI-TLIF was limited, which may reduce the power of the study. Multi-center and large-scale clinical data are needed to further study the effectiveness of MI-TLIF. In conclusion, this study confirmed MI-TLI provides a safe and effective surgical method for the treatment of spondylolisthesis.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at <https://dx.doi.org/10.21037/apm-21-2137>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/apm-21-2137>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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(English Language Editor: B. Draper)

Cite this article as: Chen Z, Wu W, Xiong H, Li G, Zhang W, Gao Y, Wang M. Systematic review and meta-analysis of the therapeutic effects of minimally invasive transforaminal interbody fusion on spondylolisthesis. *Ann Palliat Med* 2021;10(9):9848-9858. doi: 10.21037/apm-21-2137