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Original Article

Surgical management of spondylolisthesis—intentional reduction or in situ fusion: a meta-analysis

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Abstract: Objective background context: To clarify the potential difference of surgical management with intentional reduction or in situ fusion for spondylolisthesis. Methods: A comprehensive search of the NGC, the Cochrane Library, WOS, PubMed, Embase databases was conducted to identify eligible studies by the date of October 1, 2017. Three authors independently selected qualified studies, assessed methodological quality, and extracted the data. Results: 17 studies involved 992 patients were eligible for this meta-analysis (546 in reduction group and 446 in in situ fusion group). There were no significant differences in Visual Analog Scale (VAS), Japanese Orthopedic Association (JOA) scale, fusion rates and complication rates between two groups. In addition, regarding to operative time, our study indicated that in situ fusion group was associated with shorter operative time compared with reduction group. Reduction group was correlated with lower mean ODI, shorter length of stay (in low-grade), less slippage and blood loss (in high-grade) compared with in situ fusion group. Conclusion: Surgical interventions with intentional reduction did not significantly improve patient-reported outcomes, main clinical outcomes or reduce perioperative complications in low-grade spondylolisthesis. Therefore, intentional reduction may not be a requirement in the surgical management of spondylolisthesis. Randomized control studies with relatively large population and long-term follow up should be carried out to clarify this issue in the future.

Keywords: Spondylolisthesis, reduction, in situ, spinal fusion

Introduction

Spondylolisthesis is one of the most common causes of low back pain and frequently encountered by spine surgeons [1, 2]. The most frequent types of spondylolisthesis in clinical practice are isthmic spondylolisthesis and degenerative spondylolisthesis, both of which are characterized by vertebrae slippage that narrows the central canal and the foramen on either side [2-4]. According to the Meyerding grading system, vertebrae slippage within 50% was classified as low-grade spondylolisthesis, while slippage over 50% was regarded as high-grade spondylolisthesis. The neural compression caused by spondylolisthesis results in variable clinical presentation, ranging from mild to severe symptoms. Regional subluxation of the segmental lumbar may lead to the instability of the spine and severely affect patient's life [5-8].

Surgical intervention is usually suggested when conservative treatments fail or serious neurological deficits are observed or substantial and progressive slippage are presented [9]. Gill et al. came up with decompressive laminectomy in the surgical management of spondylolisthesis [10], and then, lumbar fusion was gradually adopted as the surgical standard treatment for symptomatic spondylolisthesis [11, 12]. Fusion has been achieved in multiple surgical techniques in the management of spondylolisthesis, such as posterolateral fusion (PLF), posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF) and so on [13]. Even minimally invasive spinal fusion has been indicated as a safe and effective surgical option for both isthmic and degenerative spondylolisthesis [14, 15].

Despite the advances in the surgical management of spondylolisthesis, whether to intentionally reduce the spondylolisthesis or not still remains controversial [16-24]. There is no consensus on the treatment of spondylolisthesis in guidelines. A previous meta-analysis conducted by *Longo et al.* indicated that reduction was not associated with increased clinical benefits compared with in situ fusion [25]. However, *Longo et al.* study only focused on the patients with high-grade spondylolisthesis and containing relatively less clinical items [25]. Similarly, Bai et al. [9] conducted another meta-analysis focusing on low-grade spondylolisthesis, but they only included seven studies. Still, there is no strong evidence to confirm the clinical benefits of intentional reduction of spondylolisthesis [9]. In comparison, a study by Guangyao Jiang et al. [26] is relatively comprehensive, but it is not comprehensive enough in the number of samples included and related indicators. Therefore, we conducted this comprehensive meta-analysis with available pooled data to compare the clinical difference of reduction versus in situ fusion for low-grade spondylolisthesis.

Methods

Literature search strategy

Our study was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines by using the PRISMA checklist and algorithm [27]. A complete computer-based search of the NGC, the Cochrane Library, WOS, PubMed, Embase databases was conducted up to the date of October 1, 2017. The literature search strategy was as follows: "((In situ) or fusion or arthrodesis) and (reduction) and (spondylolisthesis or spondylolysis or ((lumbar or spine or spinal) and instability))". All the retrieved articles would be checked. And reference lists were also examined for each original article in order to avoid missing relevant studies. The irrelevant articles were directly excluded by scanning the titles or abstracts. The remaining articles were then reviewed comprehensively by reading the full text. Additional contact would be made with the authors of articles to confirm data when necessary.

Inclusion criteria and exclusion criteria

One study would be included if it met all the following criteria: (1) focusing on the comparison between the operative treatment of spondylolisthesis with or without reduction; (2) retrospective or prospective studies; (3) reporting the number of patients (no less than 3 patients in each group) and outcomes of interest for each group; (4) published in English. On the contrary, reviews, letter to the editors and case reports were excluded.

Data abstraction and quality assessment

Three investigators (*Wangcheng Xie, Chaobo Feng and Yongzhao Zhao*) independently reviewed all the included studies. The following items were abstracted: family name of the first author, publication year, the etiology of spondylolisthesis (Wiltse typing), Meyerding grade, sample size, male/female ratio, average age and time of follow up. The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the quality of included studies. And NOS scores ≥6 are considered to show high-quality studies. Disagreements were resolved by consensus among the 3 investigators.

Statistical analysis

All statistical analysis was conducted with Review Manager Version 5.3.0. The mean difference (MD) or standardized mean difference (SMD) was used for summarizing continuous data, which was reported as the mean and the standard deviation. And risk ratio (RR) was used as a summary statistic for count data, which was covered as frequency and the percentage. The heterogeneity across all included studies was assessed by Cochran's Q test and Higgins I^2. The heterogeneity was significant when $P<0.05$ and/or $I^2 > 50\%$, and the random-effect model was used; if not, the fixed-effects model was applied. In addition, the funnel plot was conducted to evaluate publication bias by Review Manager Version 5.3.0 software. All p values were 2-sided and $P<0.05$ was considered statistically significant.

Results

Literature search

As shown in **Figure 1**, our initial search yielded 1480 potential literature citations. A total of 826 papers were identified after 207 non-English and 447 duplicative papers were excluded. As for the remaining papers, 786 were directly

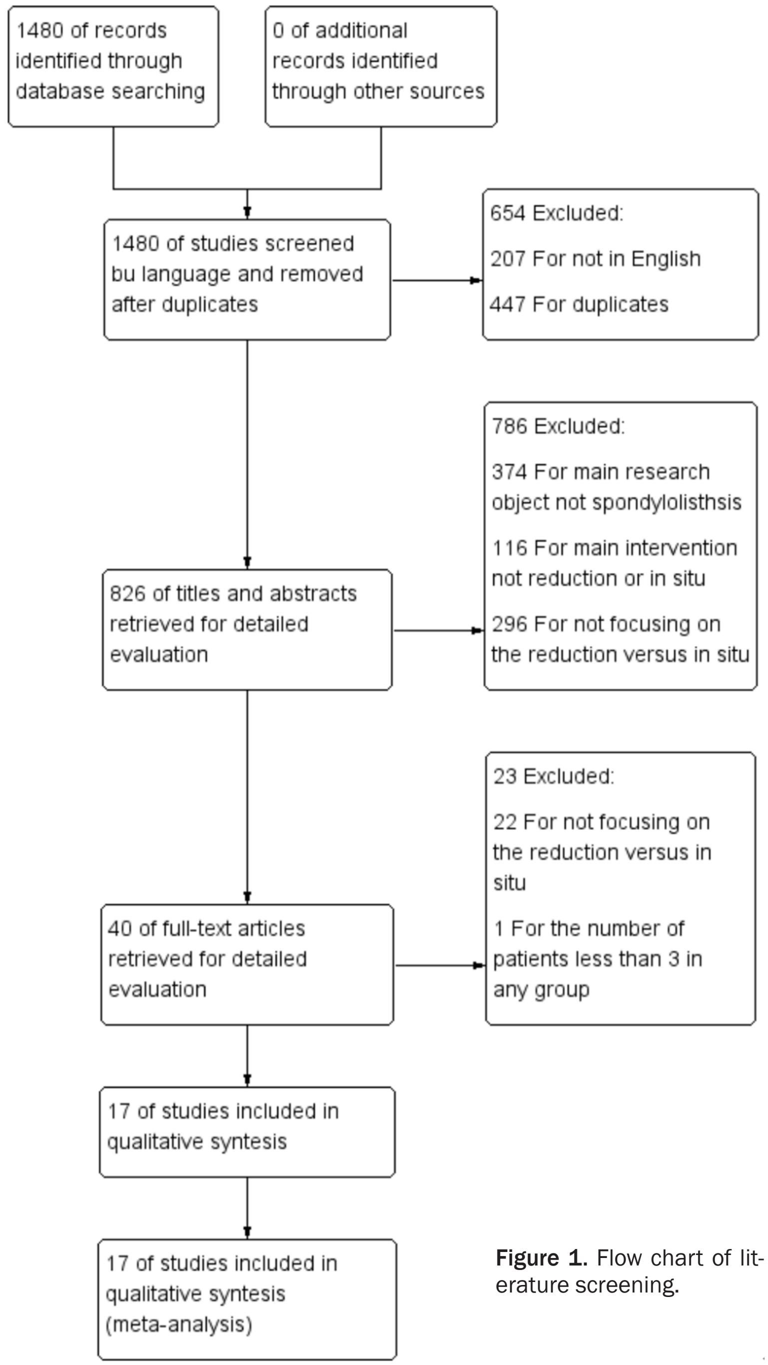

Figure 1. Flow chart of literature screening.

excluded by scanning either the titles or abstracts. For the 40 remaining potentially related studies, the full-text was carefully read for each study. 22 were excluded for not focusing on the reduction versus in situ, and 1 was excluded for the number of patients less than 3 in any group. At last, 17 studies involved 992 patients were eligible for this meta-analysis [16-18, 21-24, 28-37].

Characteristics of included studies

As listed in **Table 1**, the 7 included studies involved 992 patients [16-18, 21-24, 28-37]. Six studies were prospective studies [16, 21, 22, 32, 33, 37] and the others were retrospective studies [17, 18, 23, 24, 28-31, 34-36]. Martiniani et al. study was with the least sample size, and only contained 16 patients [31]. On the contrary, Scheer et al. study contained 282 patients with degenerative spondylolisthesis, with the largest sample size [23]. The mean age of patients in reduction group among included studies varied from 13.30 to 74.30 years old. Similarly, the mean age of patients in in situ fusion group was also different among included studies, varying from 13.90 to 73.80 years old. The male/female ratio was 192: 344 in reduction group were males and 162:272 in in situ fusion group. (The gender of one patient in *Molinari et al.* study was not be mentioned) [32]. The time of follow up was different among included studies, varying from 28.5 to 178.8months.Asforqualityassessment, the value of NOS scores was equal to or greater than 6 for each study, which indicated that all the included studies were with high quality. In additions, three studies focused on the operative treatment of degenerative spondylolisthesis [18, 22, 23], eight studies paid attention to the patients with isthmic spondylolisthesis [16, 17, 21, 30, 32, 33, 35, 36], four study contained patients with either degenerative spondylolisthesis or isthmic spondylolisthesis [24, 28, 29, 34], and two studies focused on the patients with dysplastic spondylolisthesis [31, 37].

Table 1. Characteristics of included studies

Study	Year	Study design	Etiology	Grade	Patients (n)		NOS
					Reduction	In-situ	
Audat et al.	2011	P	IS	Low	20	21	7
Benli et al.	2006	P	DCS	Low	10	10	7
				High	10	10	
Burkus et al.	1992	R	IS and DS	Low and High	24	18	6
Dewald et al.	2005	R	IS and DS	High	16	4	6
Fan et al. 1	2016	R	IS	Low	24	21	7
Fan et al. 2	2016	R	DS	Low	41	37	7
Gong et al.	2010	R	IS	Low	21	13	6
Lian et al.	2013	P	DS	Low	36	37	7
Lian et al.	2014	P	IS	Low	45	43	7
Martiniani et al.	2012	R	DCS	High	10	6	7
Molinari et al.	1999	P	IS	High	19	18	6
Molinari et al.	2002	P	IS	High	26	11	6
Muschik et al.	1997	R	IS and DS	High	30	29	6
Poussa et al.	1993	R	IS	High	11	11	7
Poussa et al.	2006	R	IS	High	11	11	7
Scheer et al.	2015	R	DS	Low	162	120	6
Tay et al.	2016	R	IS and DS	Low	30	26	7

Study	......	Male/Female (n)		Age (years)		Follow up (months)	
		Reduction	In-situ	Reduction	In-situ	Reduction	In-situ
Audat et al.	......	3:17	10:11	50.10	50.14		
Benli et al.	......	8:2	8:2	32.6	29.3	39.8	37.2
	......	8:2	8:2	32.4	34.9	36.6	38.2
Burkus et al.	......	12:12	11:7	13.30	15.87	107.87	102.39
Dewald et al.	......	6:10	1:3	33.44	35.25	79.88	76.50
Fan et al. 1	......	11:13	10:11	50.53	50.05	34.75	31.05
Fan et al. 2	......	10:31	13:24	60.95	59.81	30.78	28.95
Gong et al.	......	9:12	6:7	45.30	47.10	30.30	28.50
Lian et al.	......	14:22	14:23	74.3	73.8	33.2	33.2
Lian et al.	......	17:28	16:27	45.5	44.9	32.5	32.5
Martiniani et al.	......			19.60	19.60		
Molinari et al.	......	6:13	8:10	13.95	13.94	39.79	38.88
Molinari et al.	......	9:17	5:5	13.77	14.36		
Muschik et al.	......	13:17	11:18	14	14	67	125
Poussa et al.	......	4:7	2:9	14.9	13.9	55.5	60.1
Poussa et al.	......	3:8	3:8	14.9	14.5	178.8	174.0
Scheer et al.	......	48:114	36:84	61.68	61.88		
Tay et al.	......	11:19	5:21	56.43	58.28		

DS, degenerative spondylolisthesis; IS, isthmic spondylolisthesis; DCS, Dysplastic Spondylolisthesis; P, prospective; R, retrospective; NOS, Newcastle-Ottawa Scale.

Oswestry disability index (ODI)

The ODI was a validated questionnaire which was used to assess outcomes of interventions for pain and disability due to back disease. As shown in **Figure 2A**, seven studies reported sufficient data to extract ODI scores at last follow up. There was no obvious heterogeneity (I^2 = 0%) in low-grade group, so fixed-effect model was applied. The results showed, in low-

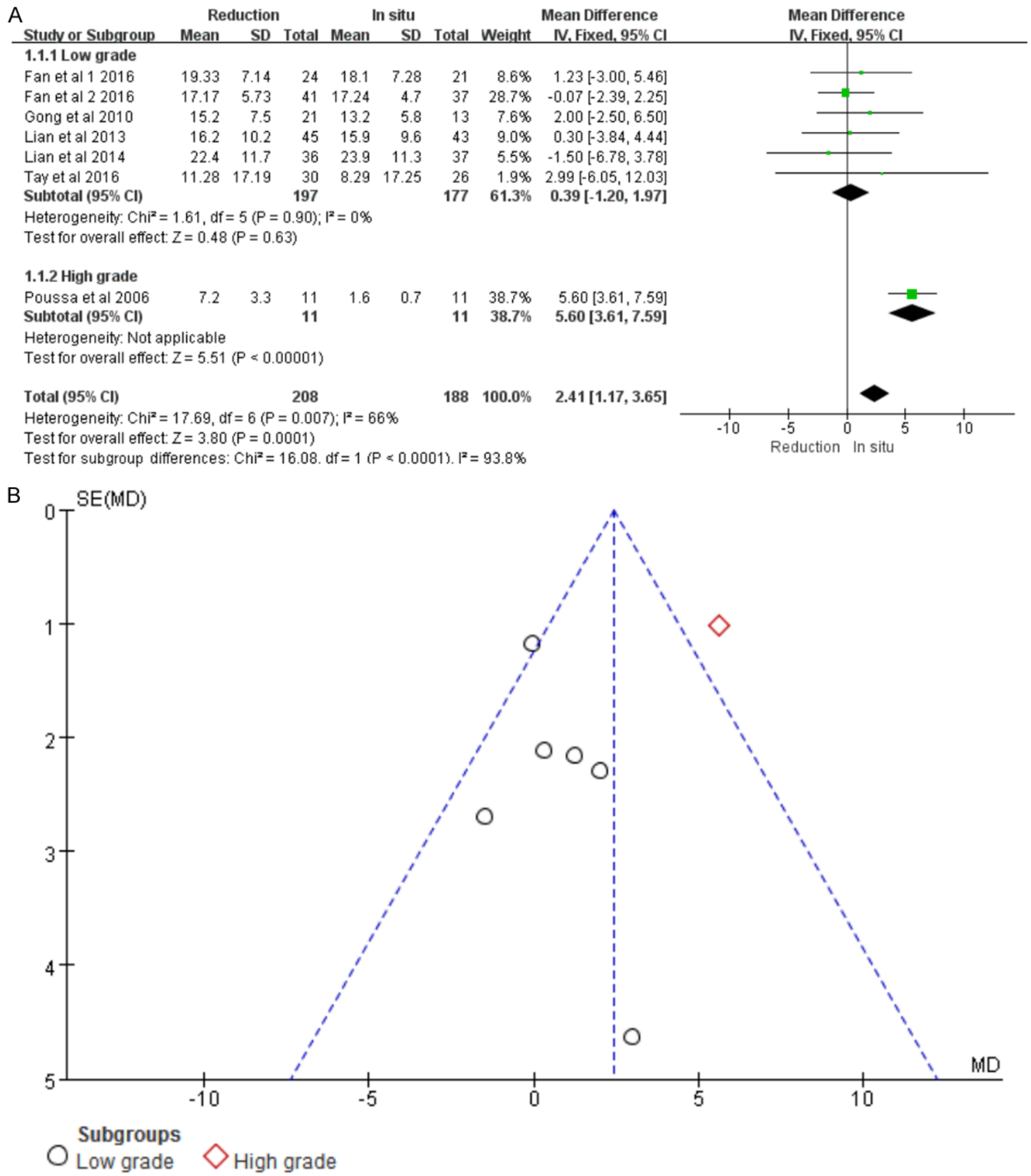

Figure 2. A. Forest plot of ODI. B. Funnel plot of ODI.

grade group, that no significant difference was observed between the reduction group and in situ fusion group (MD = 0.39, 95% CI = -1.20-1.97, P = 0.63). However, for the two sub-group, high-grade and low-grade existed large heterogeneity (I^2 = 66%). While the high-grade group only had one study, so that the comparison made little sense. No distinct publication bias was detected according to the funnel plot (**Figure 2B**). Overall, there were differences between the two groups (P = 0.0001).

Visual analog scale (VAS)

The VAS was a continuous score out of 10, with higher scores representing more pain. The VAS was covered in six studies, which were all included into this meta-analysis. The fixed-effect

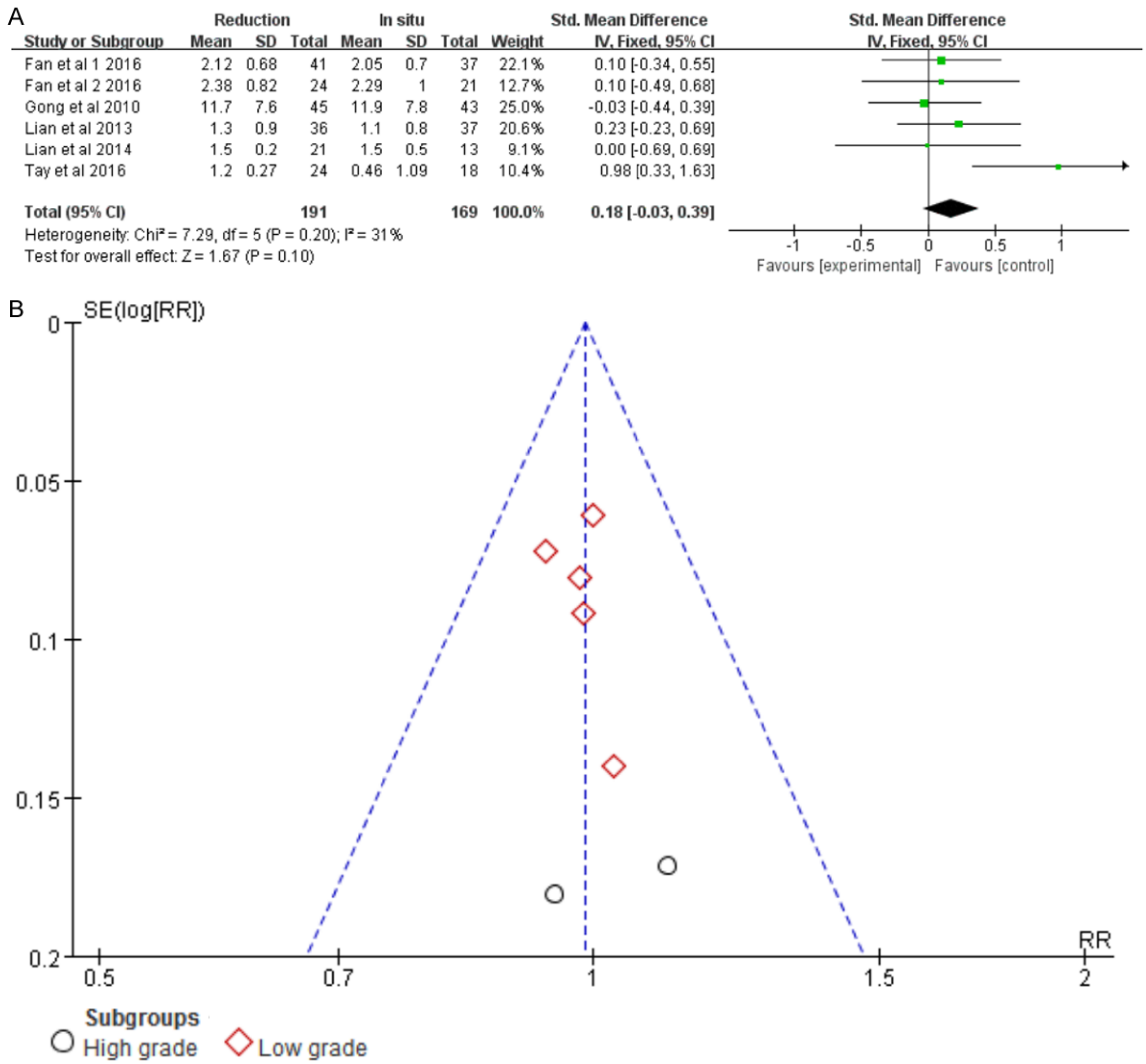

Figure 3. A. VAS of reduction group compared with in situ group in forest plot. B. VAS of reduction group compared with in situ group in funnel plot.

model was used because moderate heterogeneity was found (I^2 = 31%). And results showed there was no obvious difference between reduction group and in situ fusion group the in VAS (SMD = 0.18, 95% CI = -0.03-0.39, P = 0.10) (**Figure 3A**). The funnel plot indicated that no significant publication bias among included studies was detected (**Figure 3B**). This part of the data had not been reported in high-grade group.

Japanese orthopedic association (JOA) scale

The JOA was used to assess the disability condition. The JOA was reported in five studies, Benli IT et al. study was excluded for insufficient data reported. Therefore, four studies were all included into the analysis (**Figure 4A**). No obvious difference was observed between the patients in reduction group and patients in in situ fusion group, with random-effect model (MD = -0.15, 95% CI = -0.89-0.59, P = 0.11, I^2 = 51%). The funnel plot was generated and no significant publication bias was detected (**Figure 4B**). While, in high-grade group, this indicator was unavailable.

Estimated blood loss

Eleven studies explored the difference of estimated blood loss between two groups. However, Lian et al. 2014 was excluded for insufficient data, and ten studies were finally included into this meta-analysis. As shown in **Figure 5A**,

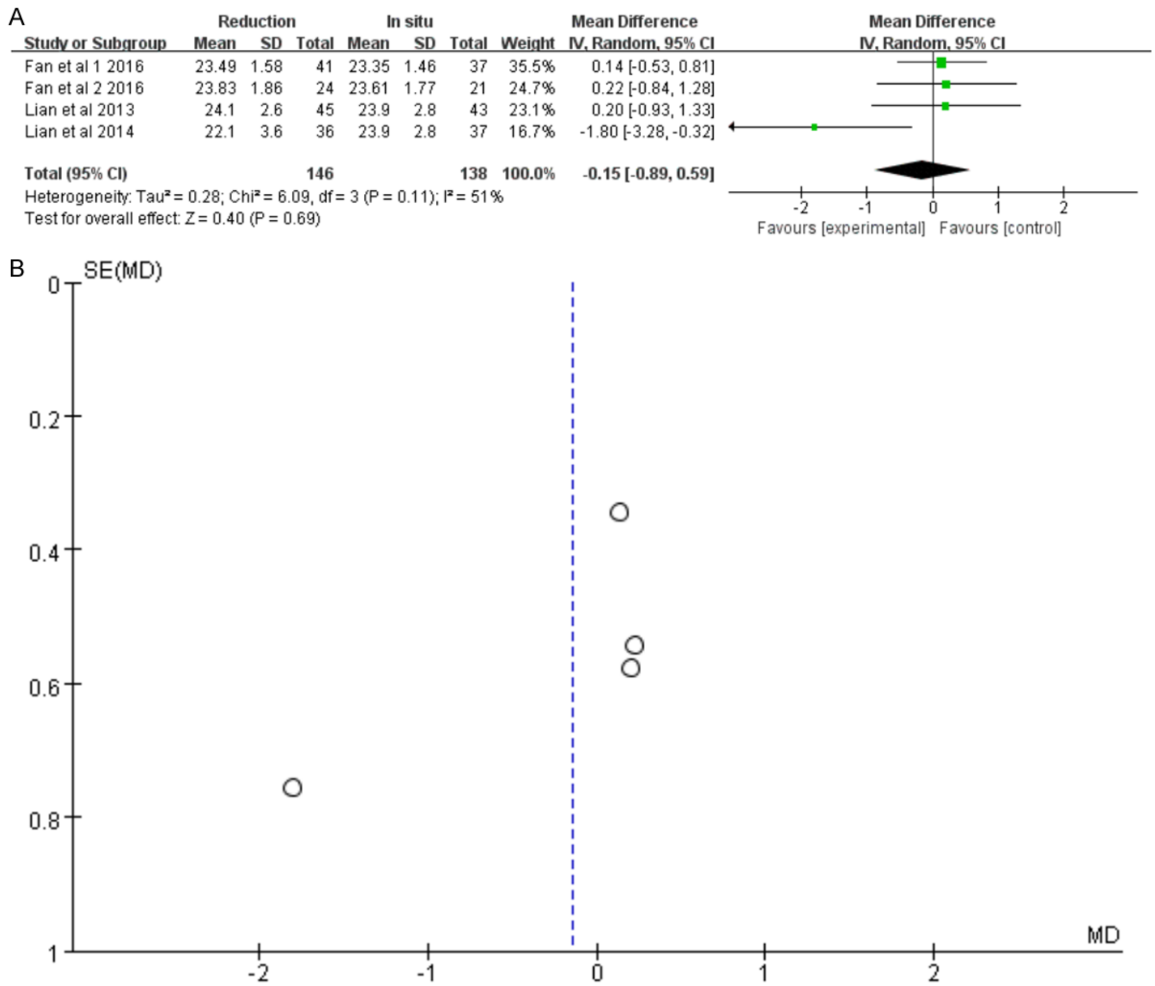

Figure 4. A. JOA scale of reduction group compared with in situ group in forest plot. B. JOA scale of reduction group compared with in situ group in funnel plot.

in view of distinct heterogeneity (I^2 = 96%), random-effect model was used. And in low-grade group, there was no obvious difference was found between the patients in reduction group and patients in in situ fusion group (SMD = 0.52, 95% CI = -0.50-1.54, *P* = 0.32. In high-grade group, the reduction group showed less blood loss compared to the in situ fusion group (SMD = 0.87, 95% CI = 0.11-1.63, *P* = 0.02).The funnel plot indicated that no significant publication bias among included studies was detected (**Figure 5B**). Overall, there was no difference between the two groups (P = 0.14).

Length of stay

The comparison of length of stay between reduction group and in situ fusion group was carried out in six studies. As shown in **Figure 6A**, random-effect model was applied for the obvious heterogeneity across included studies (I^2 = 87%). Difference was found between two groups in terms of length of stay in low-grade group (SMD = -0.47, 95% CI = -0.64-0.13, *P* = 0.05). The reduction group showed less length of stay. No obvious bias was detected among included studies (**Figure 6B**). And in high-grade group, the indicator was unavailable.

Operative time

Ten studies carried out the comparison of operative time between patients in reduction group and patients in in situ fusion group. As shown in **Figure 7A**, random-effect model was applied for the obvious heterogeneity across included studies (I^2 = 73%). In low-grade group, there was no obvious difference was found between

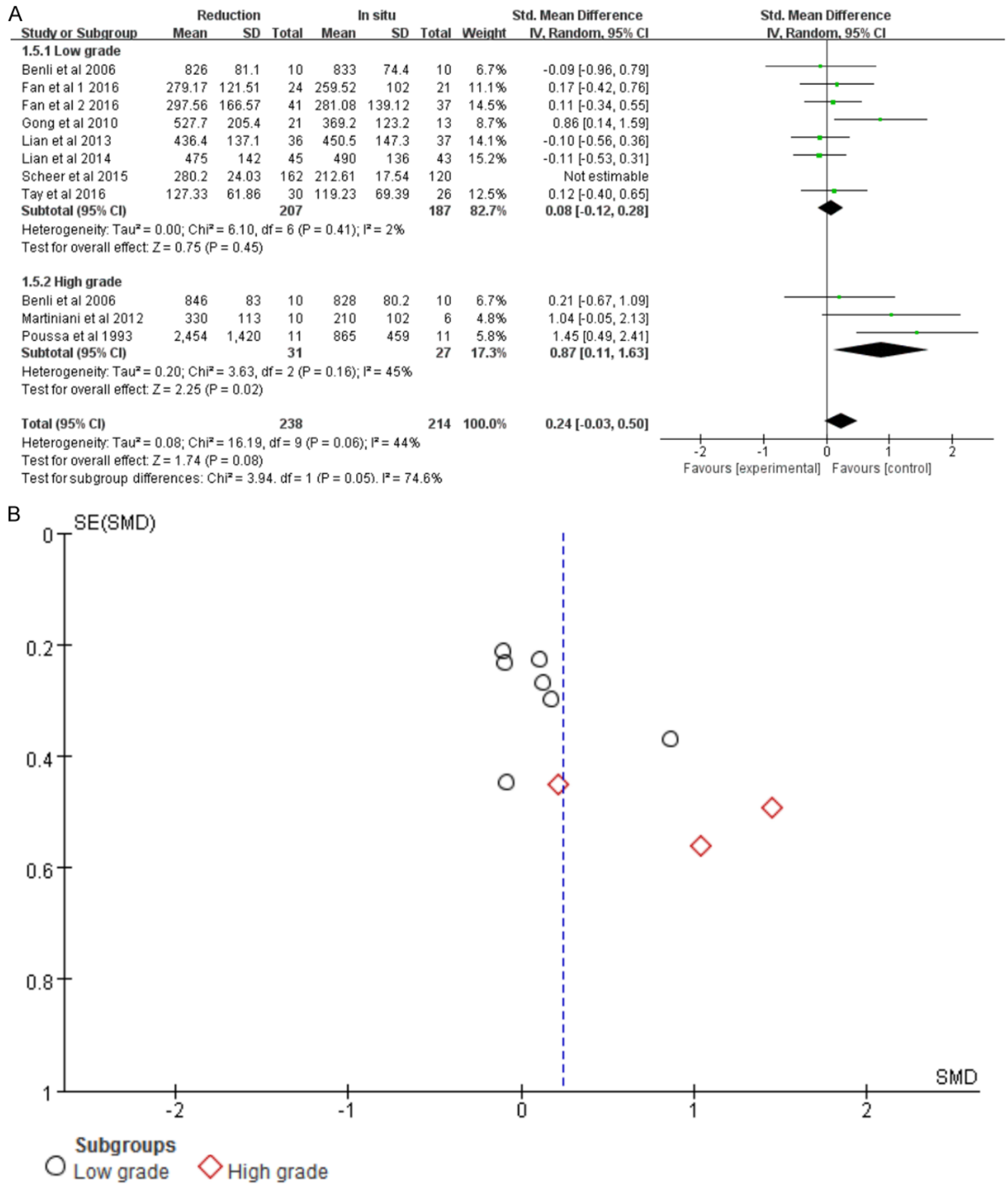

Figure 5. A. Estimated blood loss of reduction group compared with in situ group in forest plot. B. Estimated blood loss of reduction group compared with in situ group in funnel plot.

the patients in reduction group and patients in in situ fusion group (SMD = 0.13, 95% CI = -0.08-0.35, *P* = 0.23). The same result was found in high-grade group (SMD = 1.42, 95% CI = -0.44-3.27, *P* = 0.13). No obvious bias was detected among included studies (**Figure 7B**). However, in general, there were differences between the two groups (P = 0.05).

Slippage

Nine studies covered the comparison of slippage at last follow up between two groups, but Benli et al. *2006* was excluded for unclear data. Random-effect model was used according to small heterogeneity among five studies (I^2 = 60%). Less slippage was significantly observed

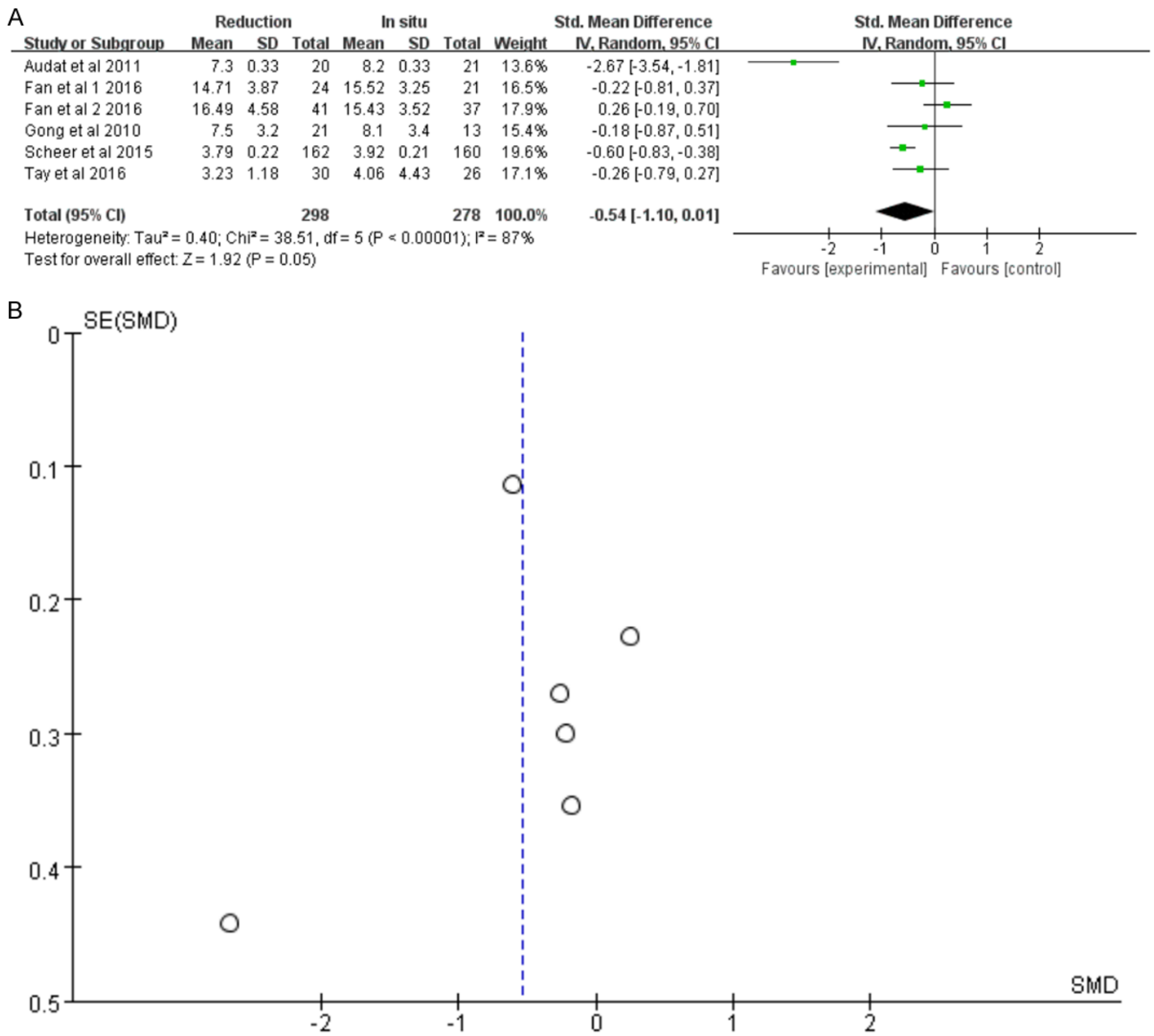

Figure 6. A. Length of stay of reduction group compared with in situ group in forest plot. B. Length of stay of reduction group compared with in situ group in funnel plot.

in reduction group compared to in situ fusion group (MD = -12.36, 95% CI = -14.15-10.57, *P*<0.00001) (**Figure 8A**). In high-grade group, the same result was found (MD = -22.73, 95% CI = -28.83-16.63, *P*<0.00001). At the same time, there are differences between the two groups in general (P<0.00001). The funnel plot indicated that no significant publication bias among included studies was detected (**Figure 8B**).

Fusion rates

Eight studies covered the fusion rates at last follow up. As shown in **Figure 9A**, Fixed-effect model was used in consideration of the obvious heterogeneity (I^2 = 77%). And the results presented that equivalent fusion rates were observed between reduction group and in situ fusion group (RR = 1.04, 95% CI = 0.96-1.12, *P* = 0.31). No publication bias was observed among included studies according to the funnel plot (**Figure 9B**). And in high-grade group, the indicator was unavailable.

Complication rates

The comparison of complications was reported in eleven studies, however, *Burkus et al. 1992* was excluded for unclear data. Fixed-effect model was used in consideration of the obvious heterogeneity (I^2 = 0%). Pooled analysis of the studies of low-grade group revealed that no significant difference was observed between reduction group and in situ fusion group (RR = 1.10, 95% CI = 0.77-1.57, *P* = 0.60) (**Figure**

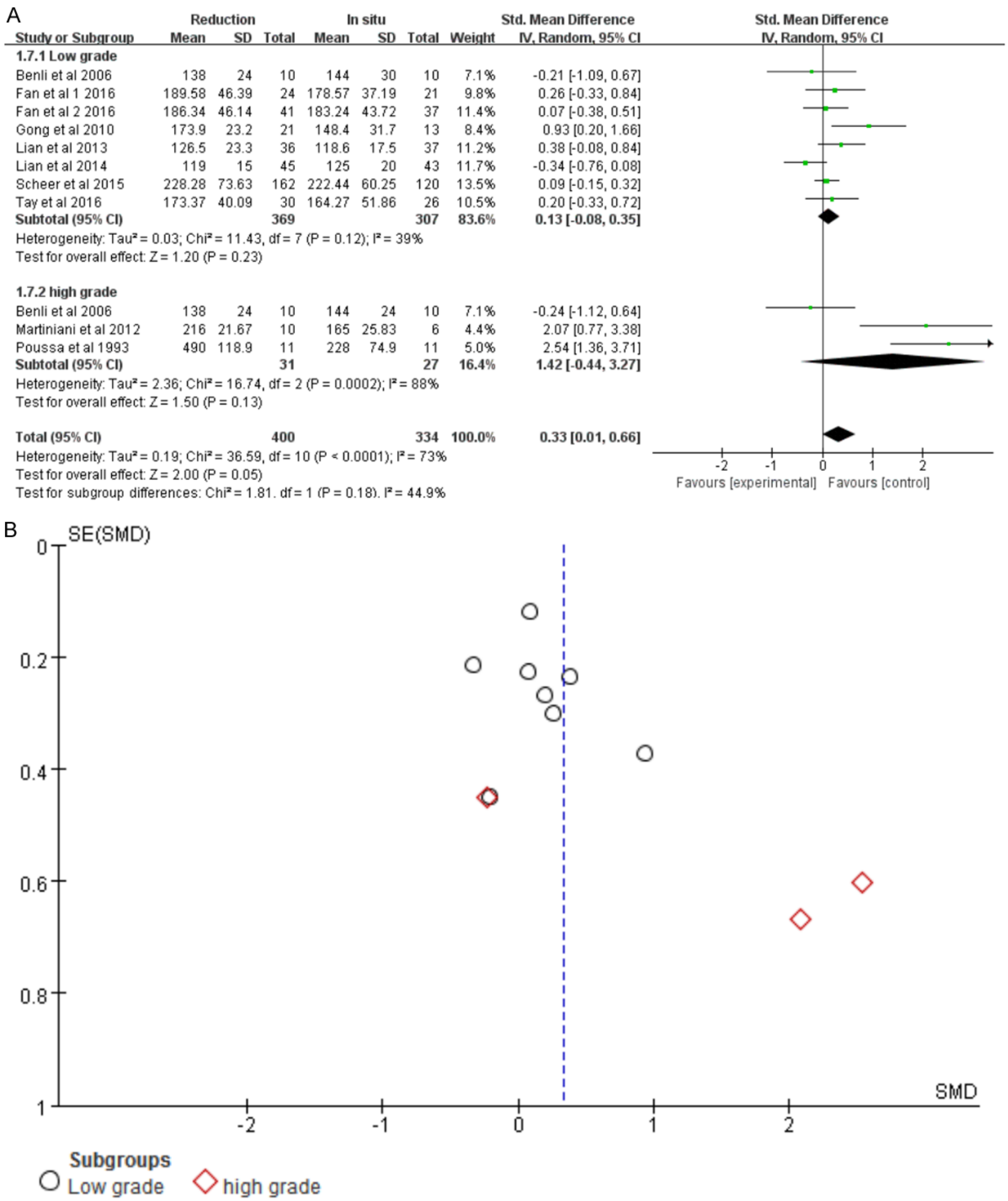

Figure 7. A. Operative time of reduction group compared with in situ group in forest plot. B. Operative time of reduction group compared with in situ group in funnel plot.

10A). In high-grade group, the same result was found (RR = 1.88, 95% CI = 0.82-4.31, *P* = 0.13). The funnel plot indicated no obvious publication bias was found (**Figure 10B**). And, there was no difference between the two groups (P = 0.30).

The rate of good and excellent

The rate of good and excellent was reported in seven studies. There was no obvious heterogeneity (I^2 = 0%) in total group, so fixed-effect model was applied. The pooled results showed

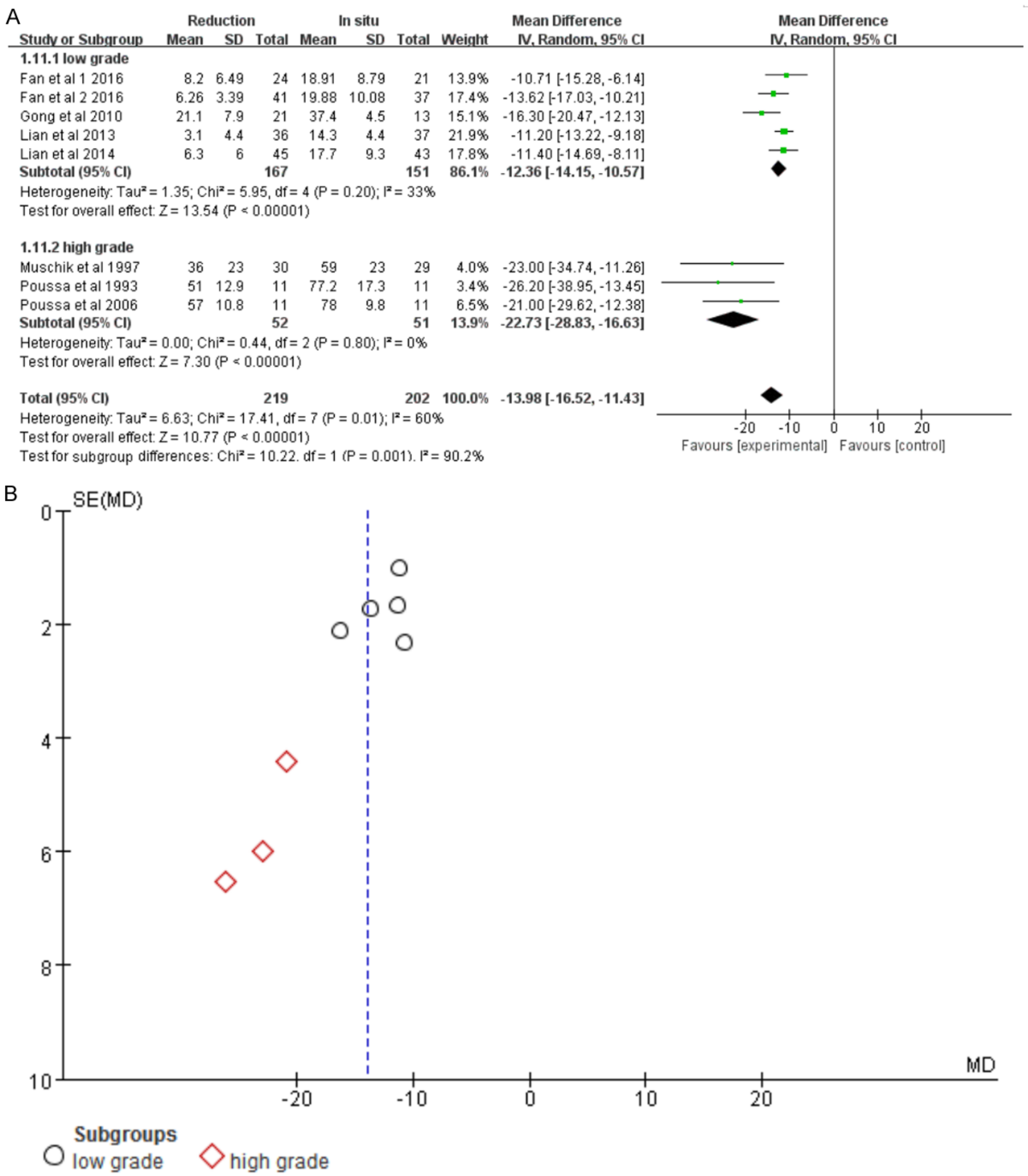

Figure 8. A. Slippage of reduction group compared with in situ group in forest plot. B. Slippage of reduction group compared with in situ group in funnel plot.

that in low-grade group, there was no significant difference between reduction group and in situ fusion group, with no heterogeneity (RR = 0.98, 95% CI = 0.91-1.07, P = 0.67, I^2 = 0%). And so was high-grade group (RR=1.04, 95% CI = 0.81-1.33, P = 0.75, I^2 = 0%) (**Figure 11A**). The funnel plot was generated and no significant publication bias was detected (**Figure 11B**). Overall, there was no difference between the two groups (P = 0.77).

Discussion

Lumbar spondylolisthesis is usually associated with low back and leg pain and surgical intervention was essential for the management of spondylolisthesis [38-41]. However, it still remained controversial whether to conduct the reduction procedure in surgical interventions for spondylolisthesis for years [17, 18, 22, 30]. To the best of our knowledge, this is the most

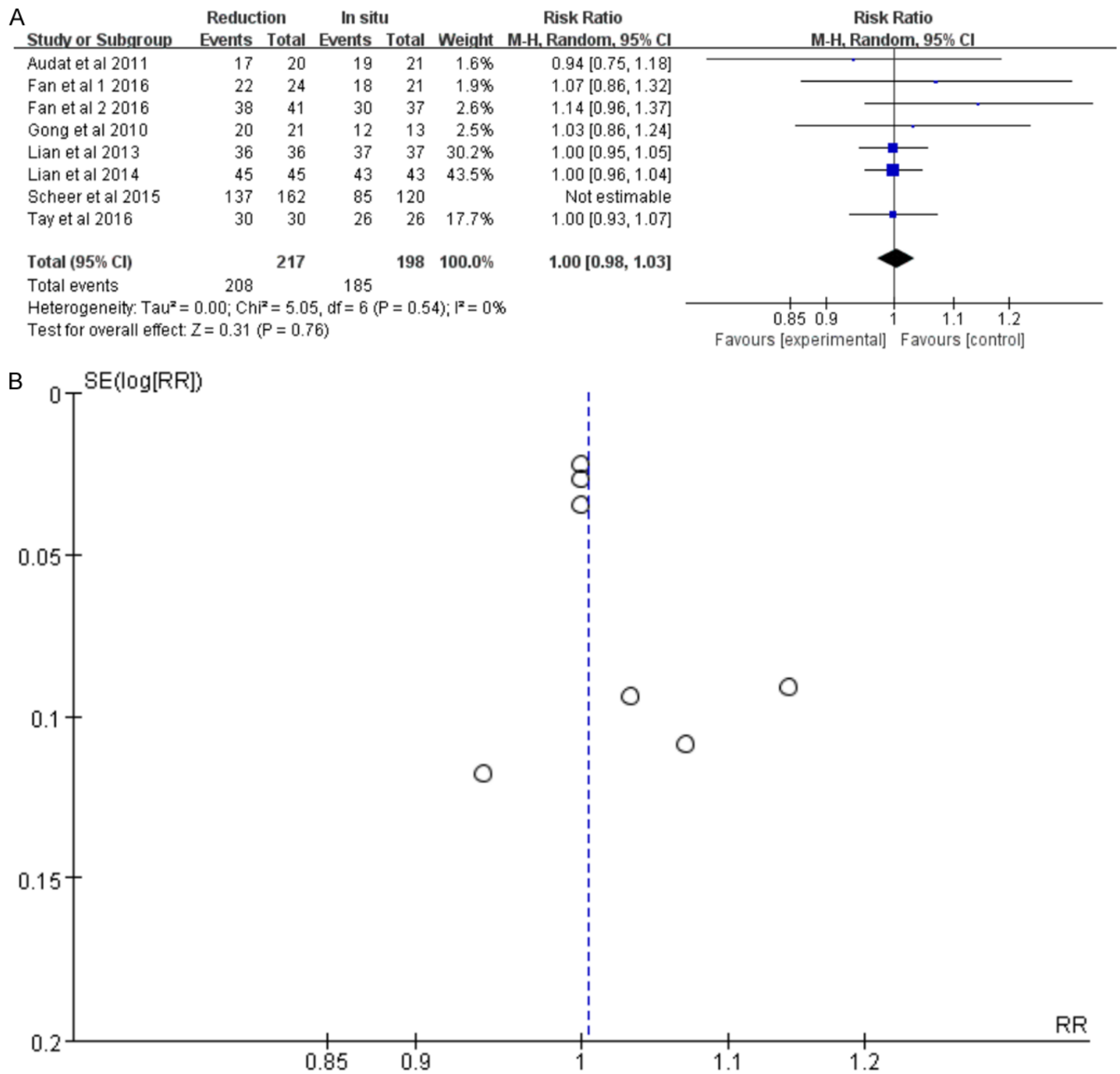

Figure 9. A. Fusion rates of reduction group compared with in situ group in forest plot. B. Fusion rates of reduction group compared with in situ group in funnel plot.

comprehensive meta-analysis with the largest pooled data.

In our study, surgical interventions with reduction were associated with comparable clinical outcomes in terms of VAS, JOA, fusion rates and complication rates compared with in situ fusion. But the ODI, estimated blood loss, length of stay, operative time, and slippage of the two groups were needed to be discussed.

As for patient-reported outcomes, the comparable results were presented between the surgical interventions with reduction and in situ fusion. Nevertheless, it should be noted that Audat et al. covered the contrary results, which indicated that reduction group was correlated with lower mean ODI compared with in situ fusion group [16]. In spite of relatively small sample size, *Audat et al.* study was a randomized and double blinded study, with similar preoperative clinical presentation between two groups [16]. Therefore, more relevant randomized controlled studies with larger sample size and long-term follow up should be carried out in future.

Our study also revealed comparable estimated blood loss between reduction group and in situ fusion group, and similar results were detected

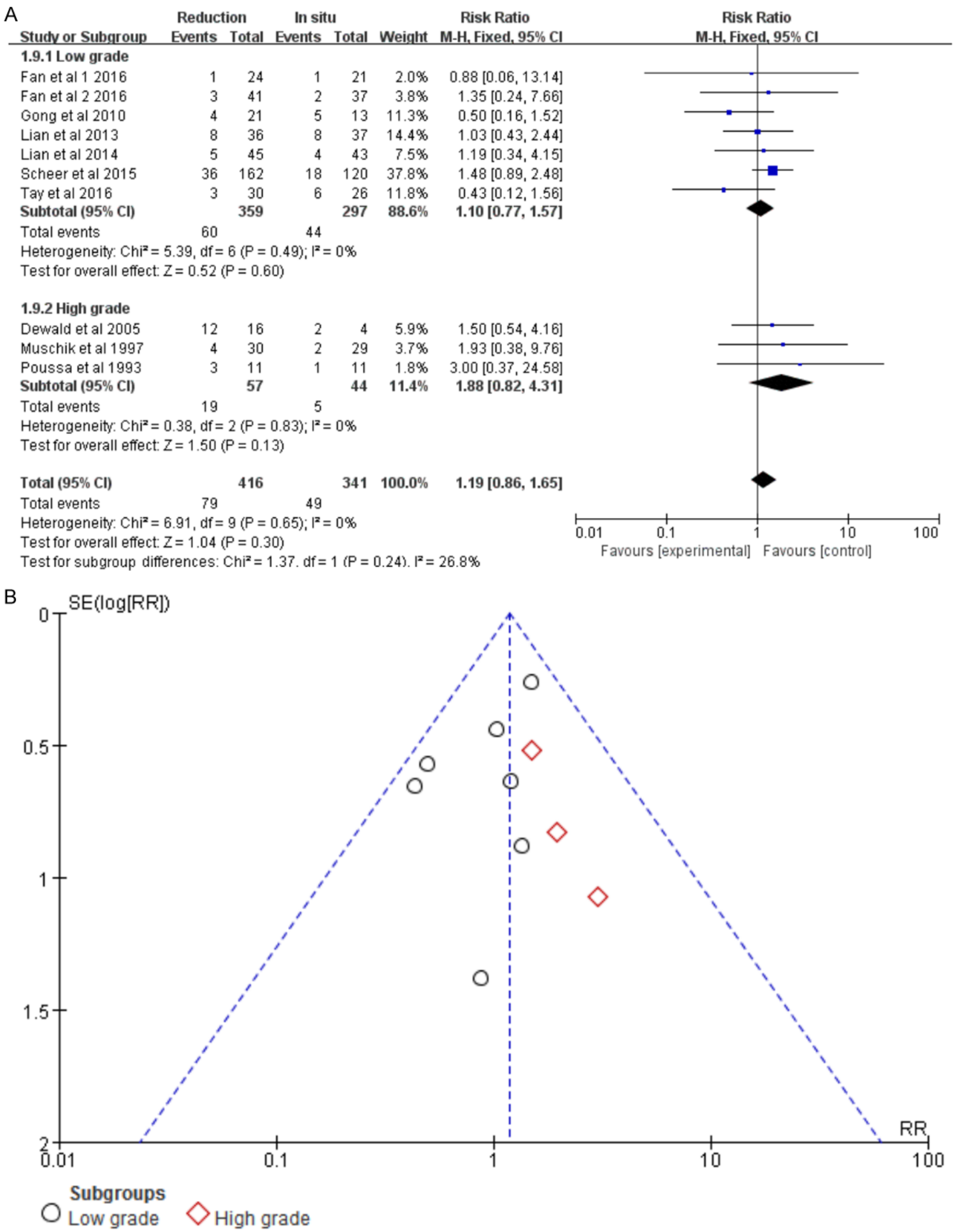

Figure 10. A. Complication rates of reduction group compared with in situ group in forest plot. a: complication rates. B. Complication rates of reduction group compared with in situ group in funnel plot. a: complication rates.

in Lian et al. study [21], however, there was less blood loss in reduction group in high-grade. As for length of stay, no difference was observed between the reduction group and in situ fusion group, but Audat et al. study reported that patients in reduction group might have shorter length of stay compared with in situ fusion group [16], which is consistent with the

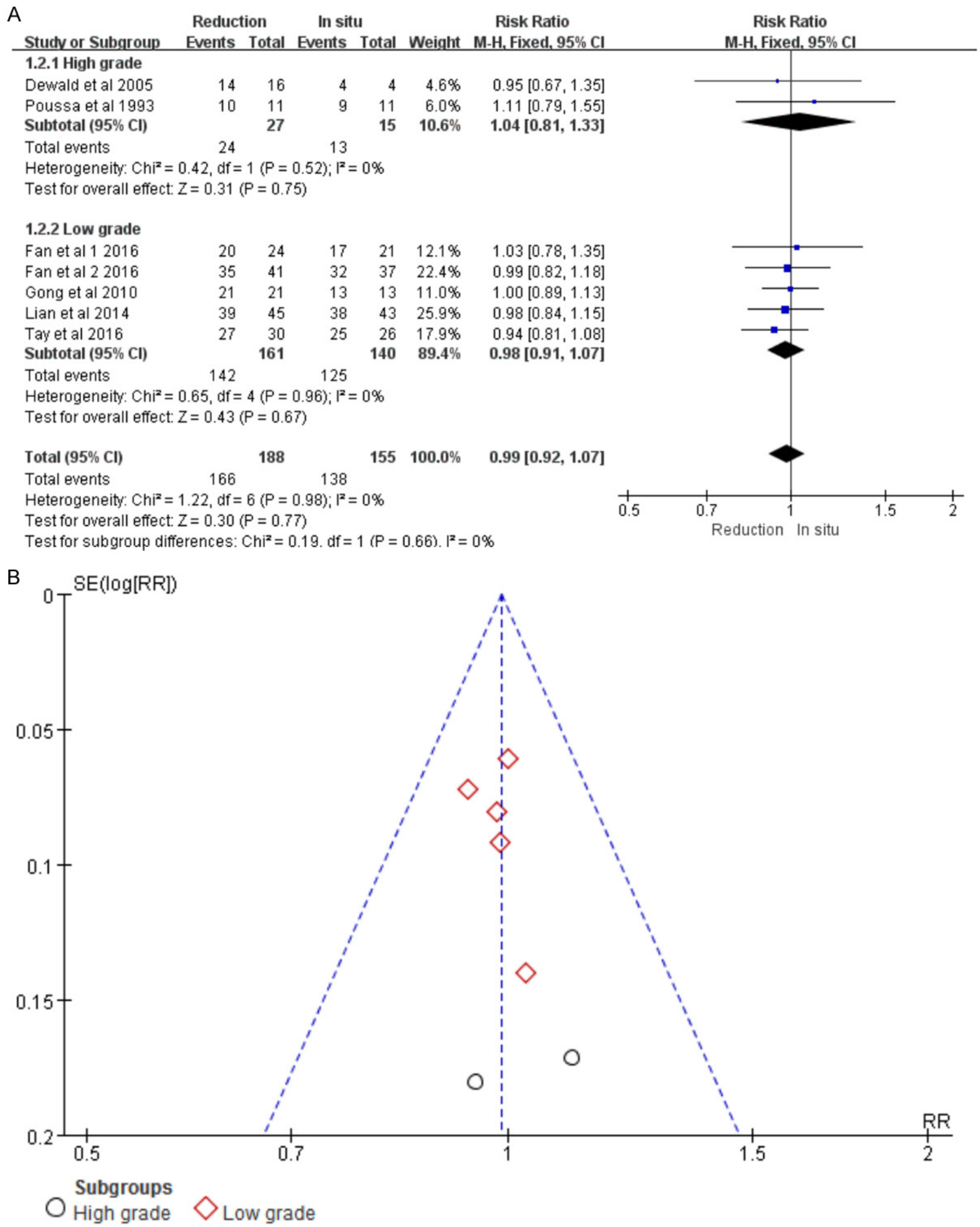

Figure 11. A. The rates of good and excellent of reduction group compared with in situ group in forest plot. B. The rates of good and excellent of reduction group compared with in situ group in funnel plot.

result of low grade. Regarding operative time, our study indicated that in situ fusion group was associated with shorter operative time compared with reduction group. And *Lian et al.* and *Audat et al.* both declared similar results [16, 21].

Less slippage was distinctly observed in reduction group in our study, and all the included studies reported the advantages of slippage in reduction group. Moreover, Lian et al. discovered that higher disc height and lower focal lordosis were found in reduction group [22]. In addition, no statistical difference was detected between the reduction group and in situ fusion group in terms of fusion rates. And high fusion rates in two groups indicated that surgical interventions with reduction or not both could significantly induce better clinical outcomes. As for complications, the infection, neuropathic pain, dural tear, cerebrospinal fluid leakage and screws pulled out were the main complications in the management of spondylolisthesis. And our results presented that reduction did not incur increased complications compared with in situ fusion group.

The highlighted strength of our meta-analysis was as follows: First, compared with the existing meta-analysis, to the best of our knowledge, our research is the most comprehensive. Two surgical methods and high-grade spondylolisthesis and low-grade spondylolisthesis were included. Second, seventeen studies with relatively high quality were included into this meta-analysis, therefore, the results were convincing. Third, this meta-analysis was comprehensive because several clinical items were analyzed, such as ODI, VAS, JOA, estimated blood loss, length of stay and so on. Nonetheless, our meta-analysis is not without limitations. First, the population in some analyses was so small, including ODI, VAS and JOA. Therefore, the relevant conclusion should be used with caution. Second, because all the data was extracted from the published papers, so the individual data was unavailable. Third, the surgical interventions were different, which might influence the clinical outcomes.

In conclusion, surgical interventions with reduction did not significantly improve patient-reported outcomes, main clinical outcomes or complications in low-grade spondylolisthesis. Therefore, the intentional reduction may not be a requirement in the surgical management of spondylolisthesis. However, in view of the limitations listed above, more randomized control studies with relatively larger population and long-term follow up should be carried out to clear this issue in future.

Disclosure of conflict of interest

None.

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