

Application of 3D-printed porous titanium interbody fusion cage vs. polyether ether ketone interbody fusion cage in anterior cervical discectomy and fusion: A systematic review and meta-analysis update

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Abstract. The present study aimed to compare the differences between 3D-printed porous titanium and polyether ether ketone (PEEK) interbody fusion cages for anterior cervical discectomy and fusion (ACDF). Literature on the application of 3D-printed porous titanium and PEEK interbody fusion cages for ACDF was searched in the PubMed, Web of Science, Embase, China National Knowledge Infrastructure, Wanfang and VIP databases. A total of 1,181 articles were retrieved and 12 were finally included. The Cochrane bias risk assessment criteria and Newcastle-Ottawa scale were used for quality evaluation and Review Manager 5.4 was used for data analysis. The 3D cage group was superior to the PEEK cage group in terms of operative time [mean difference (MD): -7.68; 95% confidence interval (CI): -11.08, -4.29; $P < 0.00001$], intraoperative blood loss (MD: -6.17; 95%CI: -10.56, -1.78; $P = 0.006$), hospitalization time (MD: -0.57; 95%CI: -0.86, -0.28; $P = 0.0001$), postoperative complications [odds ratio (OR): 0.35; 95%CI: 0.15, 0.80; $P = 0.01$], C2-7 Cobb angle

(MD: 2.85; 95%CI: 1.45, 4.24; $P < 0.0001$), intervertebral space height (MD: 1.20; 95%CI: 0.54, 1.87; $P = 0.0004$), Japanese Orthopaedic Association Assessment of Treatment (MD: 0.69; 95%CI: 0.24, 1.15; $P = 0.003$) and visual analogue scale score (MD: -0.43; 95%CI: -0.78, -0.07; $P = 0.02$). The difference was statistically significant, while there was no significant difference between the two groups in terms of fusion rate (OR: 1.74; 95%CI: 0.71, 4.27; $P = 0.23$). The use of 3D-printed porous titanium interbody fusion cage in ACDF has the advantages of short operation time, less bleeding loss, shorter hospitalization time and fewer postoperative complications. It can better maintain the cervical curvature and intervertebral height, relieve pain and accelerate postoperative functional recovery.

Introduction

Cervical spine disease is very common in modern times and can seriously affect people's lives. In severe cases, it may cause weakness or numbness in the limbs. Surgery is often required in patients who do not respond to conservative treatment and have progressively worsening symptoms. Anterior cervical discectomy with fusion (ACDF) has been recognized as one of the most effective treatments for cervical spine disorders (1). ACDF can directly relieve compression in the front of the spinal cord, including the herniated intervertebral discs, hyperplastic osteophytes behind the vertebral body and thickened posterior longitudinal ligaments. It can maintain the physiological curvature of the cervical spine, restore the height of the intervertebral space and improve cervical spine stability. Decompression, bone grafting and fusion are the key aspects of ACDF. After discectomy, fusion cages need to be implanted to restore spinal stability. The fusion effect is directly affected by the composition of the fusion cage. The commonly used iliac bone autograft transplantation often causes pain, numbness and other discomfort, which hinders postoperative recovery (2). It has therefore gradually been replaced by various grafts and fusion devices. The commonly used polyether ether ketone (PEEK) fusion device overcomes the disadvantages of difficult

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access to autologous iliac bone grafts and localized pain. However, because of its biological inertia, bone grafting is required to promote fusion. There are also shortcomings, such as cage sinking, large elastic modulus and stress shielding (3,4). The emergence of 3-dimensional (3D)-printed intervertebral fusion cages has introduced new possibilities. The 3D-printed porous titanium interbody fusion cage uses 3D printing technology to print the titanium alloy into a microporous structure similar to the trabecular bone structure, providing space conditions for the growth of osteocytes. The fusion cage is more suitable for the upper and lower vertebrae and can regulate the elastic modulus, which is conducive to the growth of osteocytes and has high biocompatibility (5). To date, titanium alloy 3D printing technology has been successfully applied in numerous aspects, including artificial joint replacement, 3D printing of an artificial vertebral body after vertebral resection, bone reconstruction after tumor resection (6-9). Studies have shown that 3D-printed cages can achieve good stability and bone fusion rates (10). The purpose of this meta-analysis was to compare and evaluate the efficacy of 3D-printed porous titanium cages and PEEK cages in ACDF and to explore the efficacy of 3D-printed porous titanium cages.

Materials and methods

Guideline and registration. This meta-analysis adheres to the reporting guidelines outlined in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (11), which does not require patient agreement and ethical reviews, given that all studies included in the analysis were derived from published research data. The protocol for this meta-analysis is available from the International Prospective Register of Systematic Reviews (<https://www.crd.york.ac.uk/PROSPERO/>; no. CRD42023461773).

Search strategy. The PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Web of Science (<https://www.webofscience.com/>), Embase (<https://www.embase.com/>), China National Knowledge Infrastructure (<https://www.cnki.net/>), Wanfang (<https://www.wanfangdata.com.cn/>), and VIP databases (<http://qikan.cqvip.com/>) were searched to identify relevant studies. The effectiveness and safety of 3D-printed porous titanium and PEEK interbody fusion cages in ACDF were collected from the establishment of the database to September 2023. The search keywords used were 3D printing, porous material, titanium, internal fixators, cervical vertebrae, discectomy, decompression surgery, spinal fusion and ACDF. The retrieval strategy was as follows: ('Printing, Three-Dimensional' OR 'Porous' OR 'Titanium') AND ('Internal Fixators' OR 'cage') AND ('Cervical Vertebrae' OR 'Discectomy' OR 'Decompression, Surgical' OR 'Spinal Fusion' OR 'ACDF').

Surgical techniques. The patient was placed in a supine position and a transverse incision was made in the anterior cervical region to reveal the anterior part of the vertebral body. Fluoroscopy was used to locate the diseased cervical vertebrae, fixation nails were inserted in the upper and lower vertebral bodies of the responsible interspaces and the intervertebral space was properly expanded by the distractor. This was followed by removal of the disc tissues, dealing with the

cartilaginous endplates, trying to mold to test the size of the fusion device, placing a 3D or PEEK cage of the appropriate height and angle, choosing the appropriate anterior steel plate for fixation, placing the drains and suturing the wound.

Inclusion and exclusion criteria. The inclusion criteria were as follows: i) Clinically controlled studies; ii) studies that included patients requiring surgery after failure of conservative treatment for cervical disc herniation and cervical stenosis; iii) the surgical method was ACDF; iv) studies using 3D and PEEK cages as interventions; v) studies that reported one of the following in the literature: Operative time, intra-operative blood loss, hospitalization days, complications, fusion rate, Cobb's angle, intervertebral space height, Japanese Orthopaedic Association Assessment of Treatment (JOA) (12) and visual analog scale (VAS) score (13). The exclusion criteria were as follows: i) Comorbid deformities, infections, neoplastic diseases and traumatic cervical spinal cord injury; ii) history of cervical spine surgery; iii) review of manuscripts, conferences, expert opinions, case reports and literature without access to the full text; iv) animal experiments and biomechanical studies; and v) non-case-control studies.

Data extraction and literature quality assessment. The literature was independently screened and identified for study inclusion by two researchers through the title, abstract and full text of the article. When there was a difference in opinion regarding the study, it was discussed and resolved. When necessary, a third researcher was consulted. The quality of the literature was determined according to the Cochrane Risk of Bias Assessment Criteria (14): i) Whether the experimental design used the principle of randomization; ii) whether the principle of double-blinding was used for participants, performers and measurements; iii) whether the experimental data were complete and trustworthy; iv) whether the allocation concealment method was used; v) whether the experiments used a selective method of data reporting; and vi) other biases. The quality of the included literature was assessed using the Newcastle-Ottawa Scale (NOS) (15) and categorized as low (score, <5), moderate (score, 5-7) and high (score, 8 or 9) quality.

Statistical analysis. Review Manager 5.4 (The Cochrane Collaboration) was used to process the collected data. Continuous variables were expressed as mean differences (MD) and 95% confidence intervals (CI), and dichotomous variables were expressed as odds ratios (OR) and 95% CI. Since there is always heterogeneity in intervention effects between multiple studies from different groups and geographic locations, random-effects models were adopted for the included studies, regardless of the size of I^2 . Studies were removed one by one to perform a sensitivity analysis. When the number of included studies was ≥ 10 , a funnel plot or Egger's test was used to determine whether there was publication bias. $P < 0.05$ was considered to indicate statistical significance.

Results

Basic characteristics of the included studies. A total of 1,181 related studies were obtained from the database after closely adhering to the inclusion and exclusion criteria.

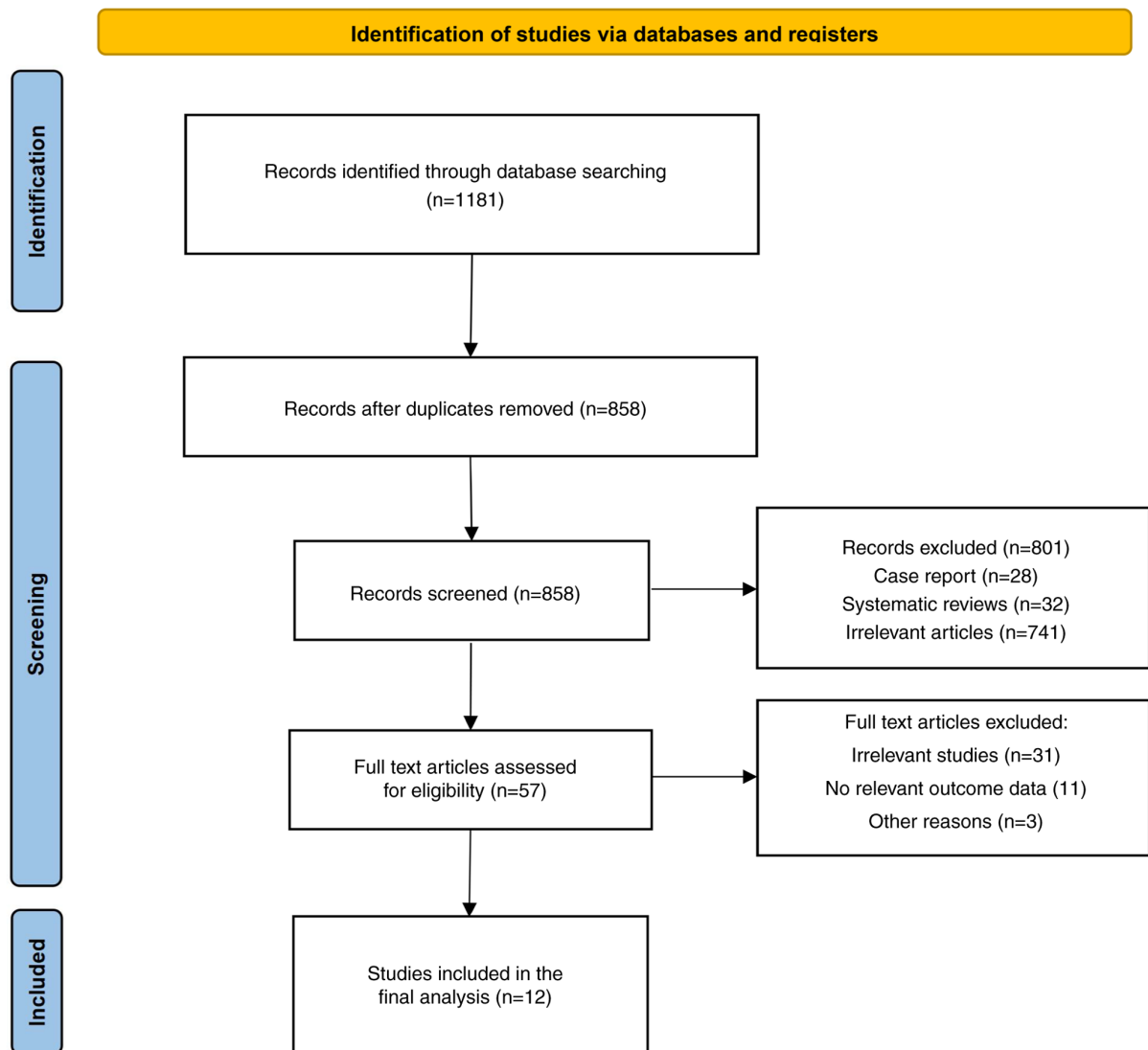


Figure 1. Flow diagram of study identification and selection.

After excluding non-case-control studies and other unrelated studies, 57 relevant studies were initially screened. Finally, the complete texts were carefully studied and 12 papers were included (10,16-25, Xu, unpublished data). The literature screening process and results are shown in Fig. 1 and the basic characteristics of the included studies are listed in Table I.

Outcome indicators of included studies. The outcome indicators included were intraoperative indicators, perioperative indicators, imaging evaluation indicators and follow-up indicators. Intraoperative indicators included operation time and intraoperative blood loss, which compared the two groups in terms of difficulty and trauma of the operation. Perioperative indicators included hospitalization days and complications, which was to compare the two groups in terms of the speed of postoperative recovery and whether it would affect the complication rate. Complications included in the study were wound infection, fusion collapse, dysphagia, screw loosening, cerebrospinal fluid leakage, neurologic injury, rejection and intraspinal hematoma. Imaging evaluation indicators included the fusion rate, Cobb's angle and intervertebral space height,

which were to evaluate the two groups in terms of spinal fusion as well as correction of spinal curves. Bony fusion was observed on radiographs as a continuous trabecular passage of bone through the fusion space. Follow-up indexes included the JOA and VAS score, which were to compare the two groups in terms of postoperative functional recovery as well as pain.

Quality assessment of included articles. A total of 12 articles were included in this study, comprising four randomized controlled trials and eight retrospective studies. A total of 758 patients were included; 380 patients received the 3D cage and 378 patients received the PEEK cage. The NOS score table was used for quality evaluation, including five articles with 8 points, four articles with 7 points, and three articles with 6 points, resulting in a total of three high-quality literature articles and seven medium-quality literature articles (Table I).

Outcomes

Perioperative indicators. Perioperative indicators included operation time, blood loss and length of hospital stay. A total of 11 studies compared the operation time of 3D-printed

Table I. General characteristics of included studies.

First author(s), year	Type of study	Country	Cases of 3D cage vs. PEEK cage, n	Mean age, years in 3D cage vs. PEEK cage group	Sex, M/F in 3D cage vs. PEEK cage group	Outcomes	Dominant group	NOS scale	(Refs.)
Arts <i>et al.</i> , 2020	Retrospective	Netherlands	49 vs. 48	50.3 vs. 49.4	23/26 vs. 25/23	⑤⑨	3D cage	6	(10)
Bai <i>et al.</i> , 2023	Retrospective	China	30 vs. 26	58.0±6.1	18/12 vs. 14/12	①②③④⑥⑧⑨	3D cage	6	(16)
Jiang <i>et al.</i> , 2022	RCT	China	45 vs. 45	47.25±9.36 vs. 45.87±10.23	25/20 vs. 21/24	①②③⑤⑥⑦	3D cage	7	(17)
Li, 2020	Retrospective	China	30 vs. 28	47.56±6.42 vs. 46.83±5.68	16/14 vs. 15/13	①②③④⑥⑦⑧⑨	3D cage	6	(18)
Li <i>et al.</i> , 2021	RCT	China	35 vs. 36	46.4±4.9 vs. 46.1±4.3	26/9 vs. 23/13	①②③④⑤⑧	3D cage	7	(19)
Liu <i>et al.</i> , 2021	RCT	China	31 vs. 32	45.72±4.58 vs. 46.23±4.39	19/12 vs. 21/11	①②③④⑥⑦	3D cage	8	(20)
Wang <i>et al.</i> , 2021	Retrospective	China	13 vs. 16	55 vs. 60	10/3 vs. 12/4	①②③④⑤⑥⑧⑨	3D cage	8	(21)
Wang <i>et al.</i> , 2023a	Retrospective	China	30 vs. 30	47.56±6.42 vs. 46.83±5.68	16/14 vs. 15/15	①②③④⑥⑦⑧⑨	3D cage	8	(22)
Wang <i>et al.</i> , 2023b	RCT	China	33 vs. 34	52.12±10.04 vs. 51.35±10.87	23/10 vs. 22/12	①②④⑤⑥⑧	3D cage	8	(23)
Xu <i>et al.</i> , 2021	Retrospective	China	36 vs. 32	53.56±6.28 vs. 54.24±7.13	19/17 vs. 15/17	①②③④⑥⑦⑧⑨	3D cage	7	(Xu, unpublished data)
Yang <i>et al.</i> , 2020	Retrospective	China	30 vs. 30	56.7±10.5 vs. 57.3±11.0	13/17 vs. 16/14	①②④⑤⑥⑦⑧⑨	3D cage	8	(24)
Zhang <i>et al.</i> , 2021	Retrospective	China	18 vs. 21	48.8±10.5 vs. 47.4±7.8	8/10 vs. 9/12	①②③④⑤⑥⑦⑧⑨	3D cage	7	(25)

Outcomes: ①, Operation time; ②, intraoperative blood loss; ③, hospitalization time; ④, postoperative complications; ⑤, fusion rate; ⑥, Cobb's angle; ⑦, intervertebral space height; ⑧, Japanese Orthopaedic Association Assessment of Treatment; and ⑨, Visual Analog Scale. RCT, randomized controlled trial; 3D, three-dimensional; PEEK, polyether ether ketone; M, male; F, female; NOS, Newcastle-Ottawa scale.

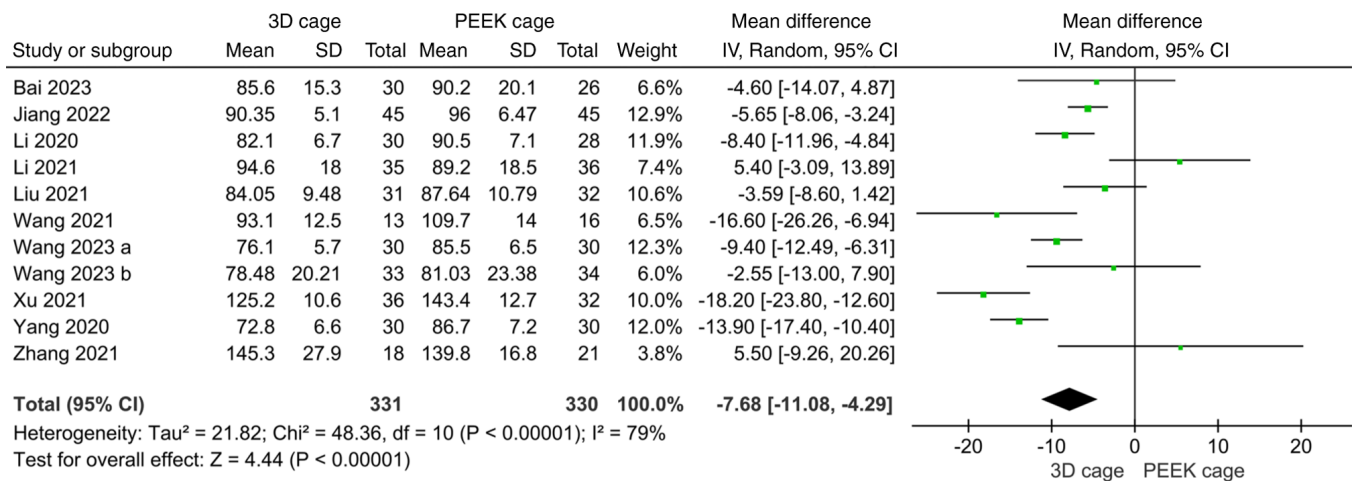


Figure 2. Forest plot for the operation time. SD, standard deviation; IV, inverse variance; random, random-effects model; df, degrees of freedom; 3D, three-dimensional; PEEK, polyether ether ketone.

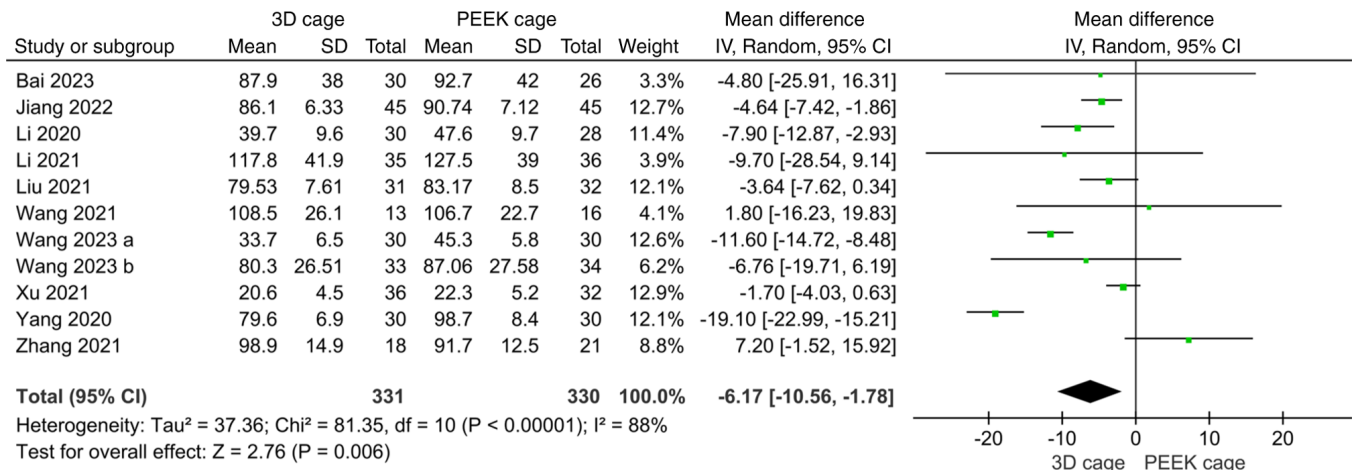


Figure 3. Forest plot for the intraoperative blood loss. SD, standard deviation; IV, inverse variance; random, random-effects model; df, degrees of freedom; 3D, three-dimensional; PEEK, polyether ether ketone.

porous titanium and PEEK cages in ACDF. The heterogeneity test showed that the heterogeneity of each study was significant ($I^2=79\%$), and the random-effects model was used for analysis. The results showed that the operation time for using 3D cage in ACDF was shorter than that for using PEEK cage, and the difference was statistically significant (MD: -7.68; 95%CI: -11.08, -4.29; $P<0.00001$; Fig. 2). Furthermore, 11 studies compared intraoperative blood loss and the heterogeneity test showed significant heterogeneity ($I^2=88\%$); accordingly, a random-effects model was used. The results showed that intraoperative bleeding was less in the 3D cage group than in the PEEK cage group (MD: -6.17; 95%CI: -10.56, -1.78; $P=0.006$; Fig. 3). A total of 9 studies compared the length of stay, with insignificant heterogeneity ($I^2=0\%$). A random-effects model was used for meta-analysis, which showed that the length of stay in the 3D cage group was shorter than that in the PEEK cage group, with the difference being statistically significant (MD: -0.57; 95%CI: -0.86, -0.28; $P=0.0001$; Fig. 4).

Postoperative complications. Altogether, 10 studies compared 3D-printed porous titanium interbody fusion

devices with PEEK interbody fusion devices for postoperative complications after ACDF, with low heterogeneity across studies ($I^2=0\%$). Using a random-effects model, the results demonstrated that application of 3D cages in ACDF was associated with fewer postoperative complications than the use of PEEK cages. The difference was statistically significant (OR: 0.35; 95%CI: 0.15, 0.80; $P=0.01$; Fig. 5).

Fusion rate. A total of seven papers reported on fusion rates, with low heterogeneity across studies ($I^2=0\%$). Meta-analysis with a random-effects model showed no significant difference in fusion rates after ACDF with a 3D or PEEK cage (OR: 1.74; 95%CI: 0.71, 4.27; $P=0.23$; Fig. 6).

Cobb angle. The Cobb angle was mentioned in 10 papers on fusion rates, of which 6 reported C2-7 Cobb angles and 4 reported fused segmental Cobb angles, with high heterogeneity ($I^2=60$ and 75% , respectively). Meta-analysis with the random-effects model indicated that the postoperative C2-7 Cobb angles in the 3D cage group were greater than those in the PEEK cage group (MD: 2.85; 95%CI: 1.45, 4.24; $P<0.0001$; Fig. 7), and the fused segment Cobb angles were not significantly different (MD: 1.31; 95%CI: -0.14, 2.76; $P=0.08$; Fig. 7).

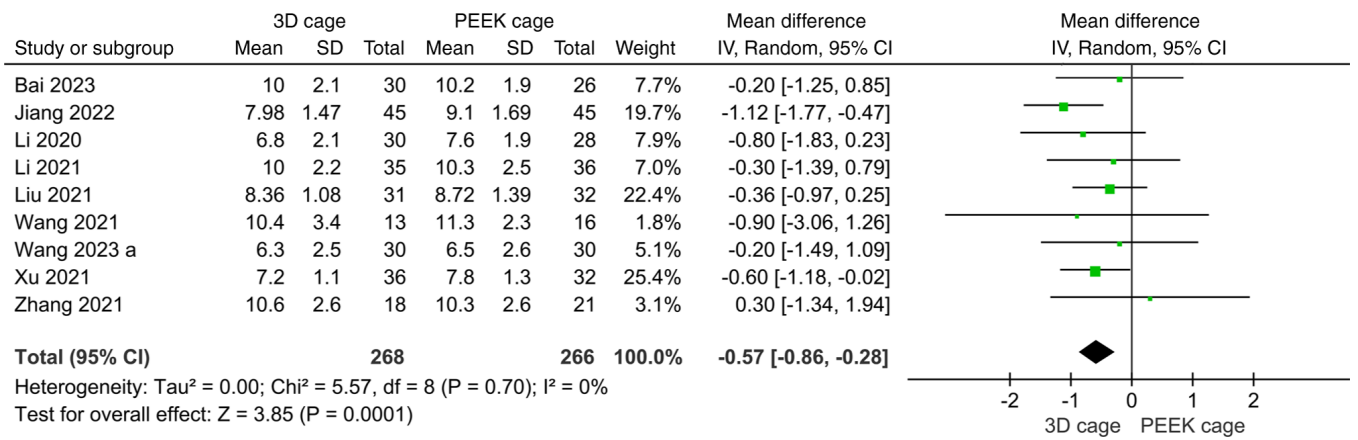


Figure 4. Forest plot for the hospitalization time. SD, standard deviation; IV, inverse variance; random, random-effects model; df, degrees of freedom; 3D, three-dimensional; PEEK, polyether ether ketone.

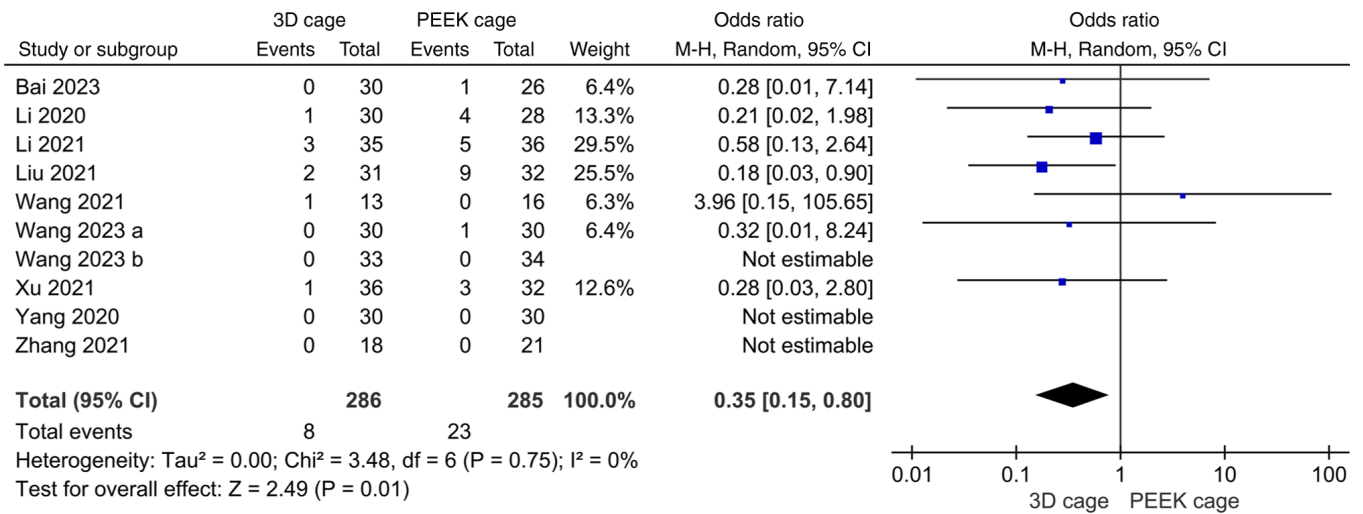


Figure 5. Forest plot for the postoperative complications. Random, random-effects model; df, degrees of freedom; M-H, Mantel-Haenszel; 3D, three-dimensional; PEEK, polyether ether ketone.

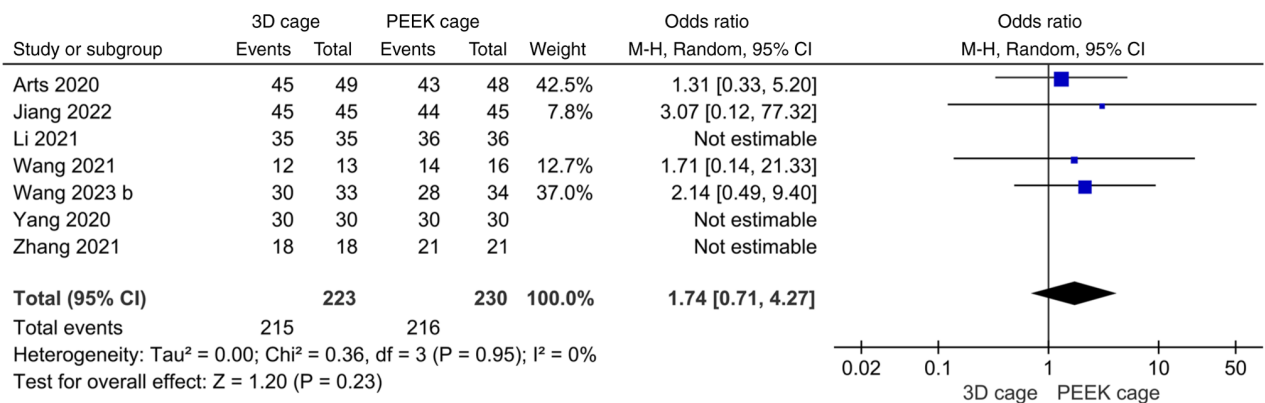


Figure 6. Forest plot for the fusion rate. Random, random-effects model; df, degrees of freedom; M-H, Mantel-Haenszel; 3D, three-dimensional; PEEK, polyether ether ketone.

Intervertebral space height. A total of seven studies reported the height of the intervertebral space. The heterogeneity was high ($I^2=91\%$) and a random-effects model was used. The results showed that the height of

the intervertebral space in the 3D cage group was greater than that in the PEEK cage group, and the difference was statistically significant (MD: 1.20; 95%CI: 0.54, 1.87; $P=0.0004$; Fig. 8).

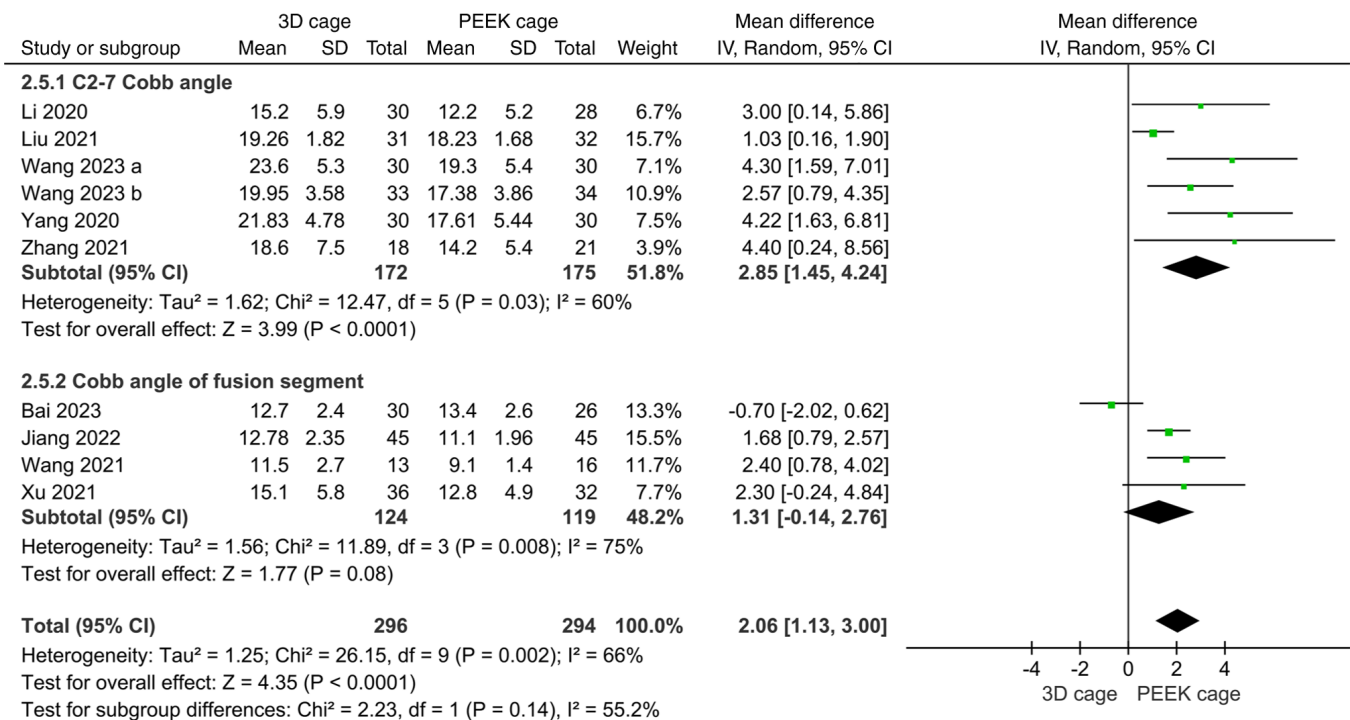


Figure 7. Forest plot for the Cobb angle. SD, standard deviation; IV, inverse variance; random, random-effects model; df, degrees of freedom; 3D, three-dimensional; PEEK, polyether ether ketone.

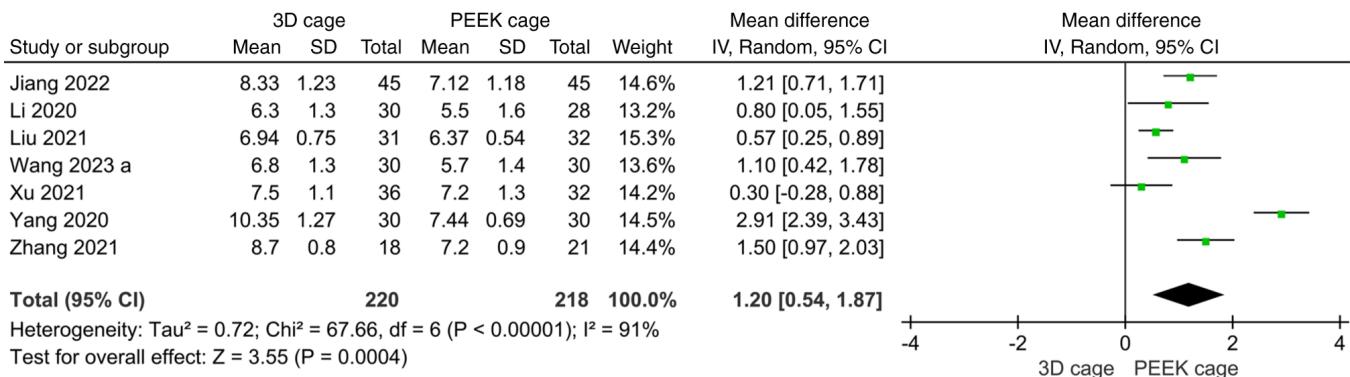


Figure 8. Forest plot for the intervertebral space height. SD, standard deviation; IV, inverse variance; random, random-effects model; df, degrees of freedom; 3D, three-dimensional; PEEK, polyether ether ketone.

JOA. A total of 9 articles compared the postoperative JOA score; the overall heterogeneity was high ($I^2=66\%$) and the random-effects model was used. The results showed that the JOA score of the 3D cage group was higher than that of the PEEK cage group and the difference was statistically significant (MD: 0.69; 95%CI: 0.24, 1.15; $P=0.003$; Fig. 9).

VAS. A total of eight papers reported results of postoperative VAS scores, with significant heterogeneity across studies ($I^2=89\%$), and a random-effects model was used. The results showed that the postoperative VAS scores were lower in the 3D cage group than in the PEEK cage group, with a statistically significant difference (MD: -0.43; 95%CI: -0.78, -0.07; $P=0.02$; Fig. 10).

Publication bias and sensitivity analysis. Nine outcome indicators of operative time, intraoperative blood loss, hospital

days, complications, fusion rate, Cobb angle, intervertebral space height, JOA and VAS were analyzed; utilizing the statistical program Review Manager 5.4, publication bias analysis was carried out (Figs. 11 and 12). A total of 4 studies (17,19,20,23) were randomized controlled trials using random number sequences with low-risk of selection bias and no allocation concealment; only one paper (20) mentioned blinding of the study, while the others did not mention blinding; 1 paper (13) had incomplete data on outcome indicators; one paper (16) had problems with selective reporting of data; and finally, no other risks of bias were identified. The findings demonstrated no clear publication bias because the funnel plots for each item were symmetrical (Fig. 13). Although there were seven studies related to the fusion rate, only four were included in the analysis because three of the studies had a 100% fusion rate, and these data

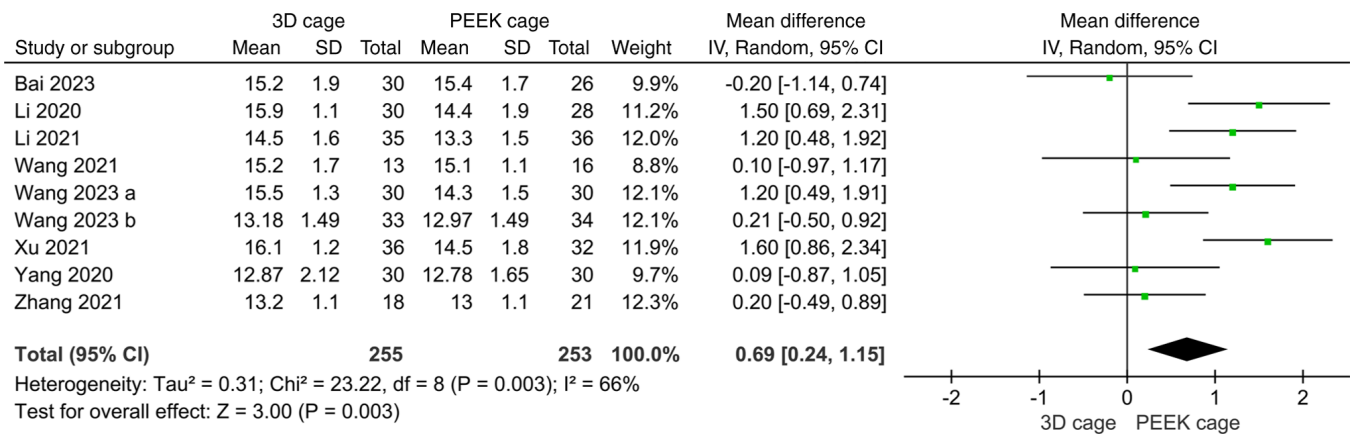


Figure 9. Forest plot for the Japanese Orthopaedic Association Assessment of Treatment. SD, standard deviation; IV, inverse variance; random, random-effects model; df, degrees of freedom; 3D, three-dimensional; PEEK, polyether ether ketone.

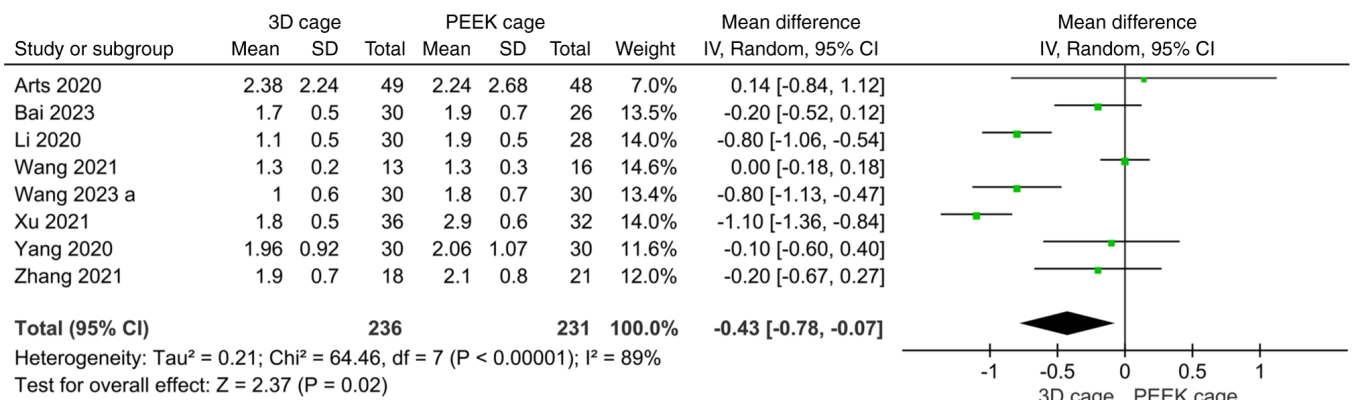


Figure 10. Forest plot for the visual analog scale score. SD, standard deviation; IV, inverse variance; random, random-effects model; df, degrees of freedom; 3D, three-dimensional; PEEK, polyether ether ketone.

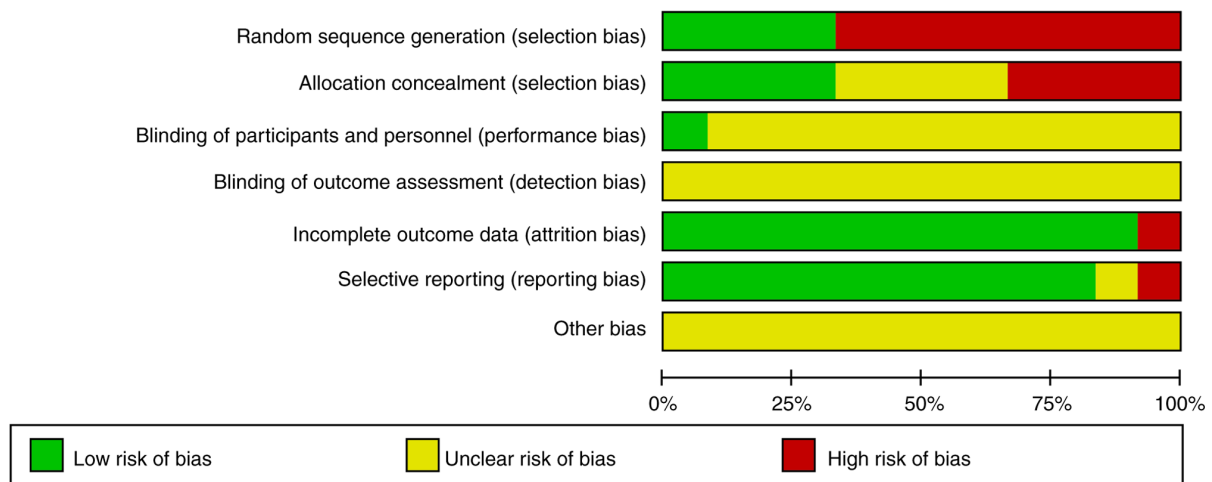


Figure 11. Overall risk of bias assessment of the studies included in the present meta-analysis.

could not be used for meta-analysis; however, there was low heterogeneity, indicating good stability of the results. While the heterogeneity of operation time, intraoperative blood loss, Cobb angle, intervertebral space height, JOA and VAS scores was high, after sensitivity analysis, the results of the

meta-analysis showed no directional change, indicating that the results of the studies were relatively stable and reliable. The metrics with high heterogeneity in this study included operative time, blood loss, Cobb angle, intervertebral space height, JOA and VAS scores. Among them, the heterogeneity

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Arts2020	⊖	?	?	?	⊖	+	?
Bai2023	⊖	?	?	?	+	⊖	?
Jiang2022	+	+	?	?	+	?	?
Li2020	⊖	⊖	?	?	+	+	?
Li2021	+	+	?	?	+	+	?
Liu2021	+	+	+	?	+	+	?
Wang2021	⊖	⊖	?	?	+	+	?
Wang2023a	⊖	⊖	?	?	+	+	?
Wang2023b	+	+	?	?	+	+	?
Xu2021	⊖	?	?	?	+	+	?
Yang2020	⊖	⊖	?	?	+	+	?
Zhang2021	⊖	?	?	?	+	+	?

Figure 12. Risk of bias assessment of the specific studies included in the present meta-analysis.

was significantly reduced after the removal of surgical time from 3 studies (19,24, Xu, unpublished data), blood loss from 3 studies (22,24,25), Cobb angle from 2 studies (16,20), intervertebral space height from 2 studies (24,25) and JOA from 3 studies (16,18, Xu, unpublished data), and the I^2 was 48, 0, 0, 49 and 49% (Figs. 14-18, respectively). By contrast, the decrease in heterogeneity of VAS scores after sensitivity analyses was not significant.

Discussion

Cervical spine disorders are becoming increasingly common in populations with changes in living habits and are increasingly seen in younger populations. Currently, the main treatments are rehabilitation, conservative treatment and surgery, and severe cervical spine disease often requires surgery (26). ACDF is popular in clinical practice and can directly decompress the posterior compression of the vertebral body from the cervical incision approach, which can remove the posterior longitudinal ligament and hyperplastic bone and rebuild the cervical curvature and stability. There are various problems in clinical practice, such as autologous or allogeneic bone transplantation, fusion cages of various materials and artificial intervertebral discs. The type of fusion device used during surgery is problematic. The 3D-printed fusion cage has characteristics that the previous fusion cage does not have; it is more matched with the anatomical structure of the patient's vertebral body and the mechanical structure is more stable. The 3D-printed porous titanium interbody fusion cage has an interconnected microporous structure that simulates the structure of the trabecular bone, which not only regulates the elastic modulus but also reduces stress shielding. The microporous structure and rough surface of the 3D cage also provide better growth conditions for bone tissue adhesion, proliferation and differentiation, which are conducive to intervertebral fusion (27). However, the PEEK cage has few hydrophilic groups, high biological inertia and a smooth surface, and can easily be wrapped by fibrous tissue, which cannot provide conditions for the adhesion of osteoblasts, resulting in weak osseointegration ability (28). Furthermore, the bone blocks implanted in PEEK cages are mainly allogeneic. The affinity and bone conduction ability of allogeneic bone cells are weak, and osteoblasts have difficulty adhering to and differentiating on their surfaces (29). At present, titanium alloy materials are widely used in the field of 3D-printed implants. It has the advantages of high histocompatibility, strength, corrosion resistance, reduced postoperative immune rejection and fusion collapse (30,31). The high connectivity and porosity of the porous titanium structure promote the adhesion of osteoblasts, which have a role in bone growth and tissue differentiation, thus increasing the fusion rate. The fusion rate of triple-D printed porous titanium fusion devices is closely related to the porosity, which should be at least >50%, preferably in the range of 65-80%, and their structure and elastic modulus are similar to those of human bone trabeculae (32). A finite element analysis found that the modulus of elasticity decreased as the aperture size and porosity increased accordingly and found that the modulus of elasticity of a fusion with an average aperture size of 0.75 mm/porosity of 72.8% was within the range of the modulus of elasticity of natural bone and was stable after implantation, which is beneficial to the recovery of the human lumbar spine (33). The present study compared the efficacy of 3D-printed porous titanium and PEEK fusions in ACDF to investigate the safety and efficacy of 3D-printed cages.

In the present meta-analysis, the operation time and blood loss in the 3D-printed cage group were lower than those in the PEEK cage group, and the difference was statistically significant. This was because the PEEK cage group required repeated mold testing and bone grafting. The 3D-printed cage group underwent

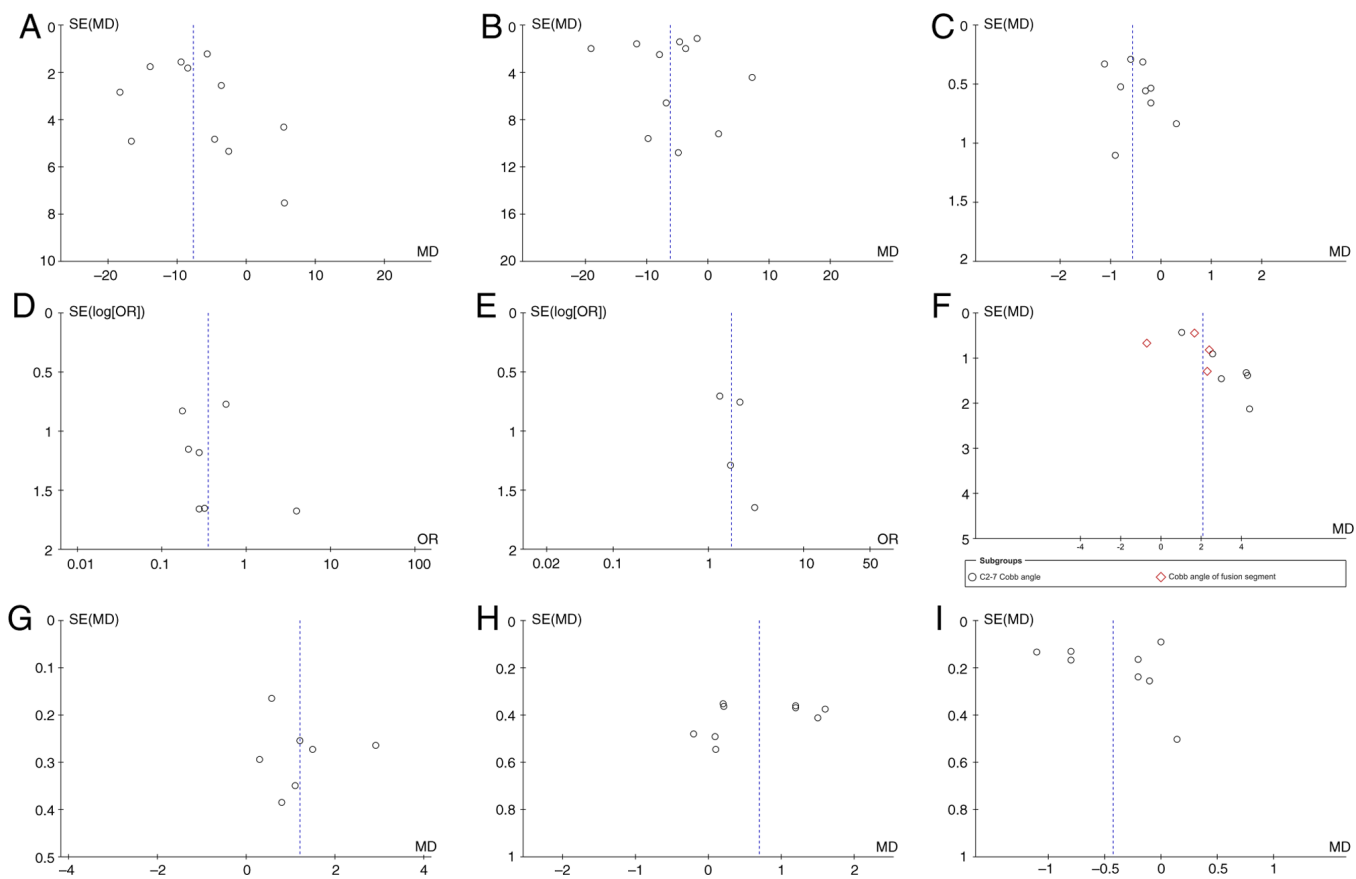


Figure 13. Funnel plots created to assess publication bias for (A) operation time, (B) intraoperative blood loss, (C) hospitalization time, (D) postoperative complications, (E) fusion rate, (F) Cobb angle, (G) intervertebral space height, (H) Japanese Orthopaedic Association Assessment of Treatment and (I) visual analogue scale score. SE, standard error; MD, mean difference; OR, odds ratio.

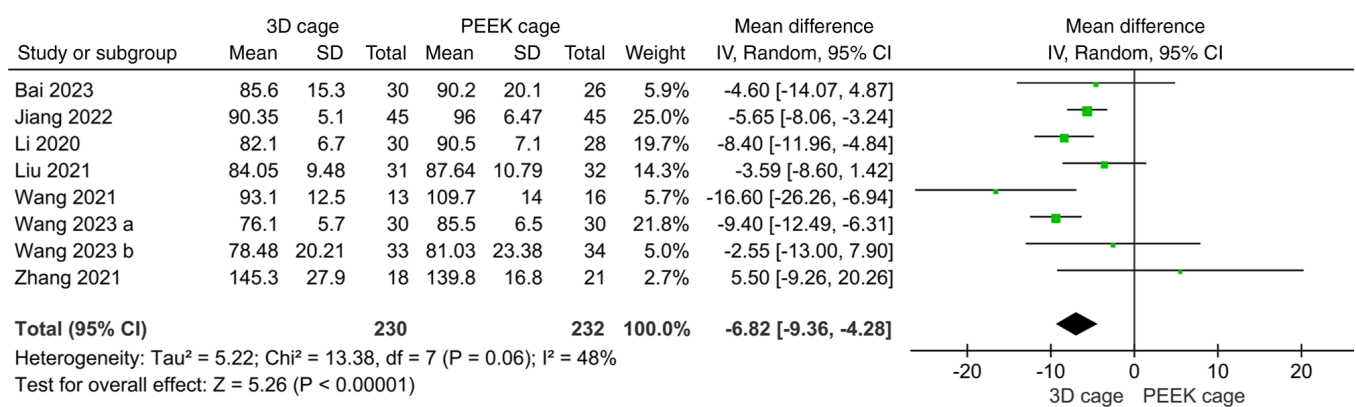


Figure 14. Forest plot after sensitivity analysis of the operation time. SD, standard deviation; IV, inverse variance; random, random-effects model; df, degrees of freedom; 3D, three-dimensional; PEEK, polyether ether ketone.

planning for the corresponding model size prior to surgery and did not require bone grafting, which is easy to operate and saves time by reducing bleeding. The 3D-printed cage group had a significantly shorter hospitalization time and fewer postoperative complications than the PEEK cage group. Intravertebral hematomas accounted for ~1/3 of the complications, while the ratio of intravertebral hematomas in the 3D-printed and PEEK cage groups was 3:7. The reason is that the 3D-printed cage has a porous structure, which is more conducive to the exclusion of hematoma; all three cases of rejection reaction were in the PEEK cage group.

The PEEK cage had high biological inertia, whereas the titanium alloy had high histocompatibility, and no rejection reactions occurred. The other 1/3 showed cage collapse, implant movement and screw loosening, while the ratio of them in the 3D-printed and PEEK cage groups was 2:9, which was significantly better than that of the PEEK cage group. The porous structure can effectively reduce the stress shielding effect of the interface between the cage and vertebral body, slow the loss of intervertebral height, provide growth conditions for the proliferation and differentiation of osteocytes, accelerate intervertebral fusion and prevent

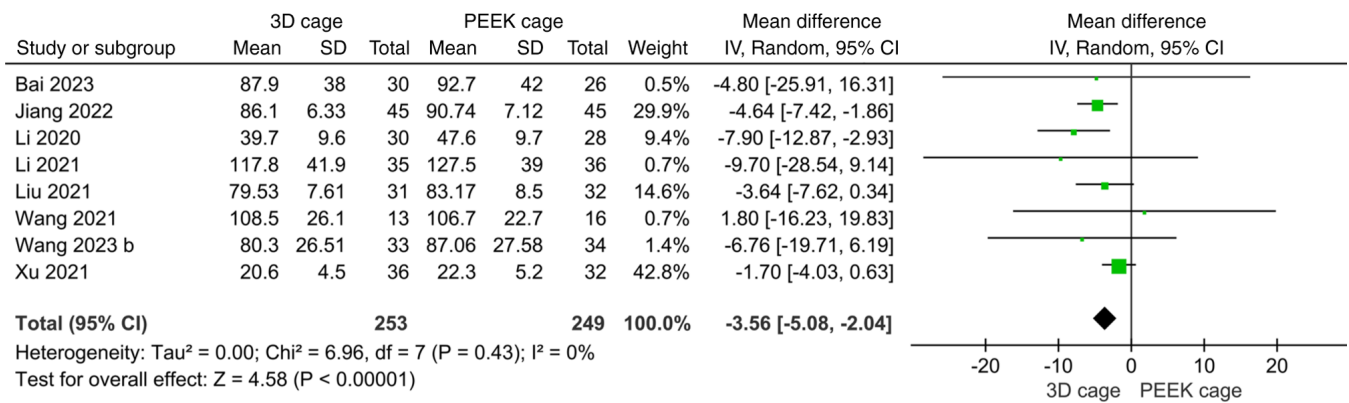


Figure 15. Forest plot after sensitivity analysis of the intraoperative blood loss. SD, standard deviation; IV, inverse variance; random, random-effects model; df, degrees of freedom; 3D, three-dimensional; PEEK, polyether ether ketone.

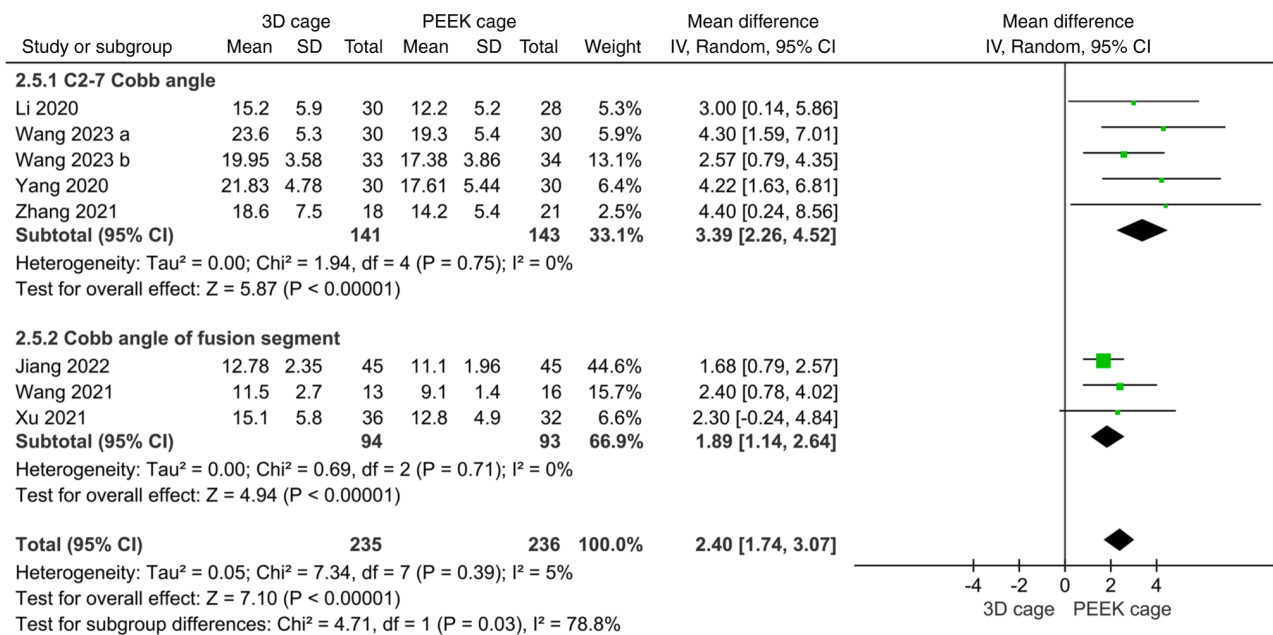


Figure 16. Forest plot after sensitivity analysis of the Cobb angle. SD, standard deviation; IV, inverse variance; random, random-effects model; df, degrees of freedom; 3D, three-dimensional; PEEK, polyether ether ketone.

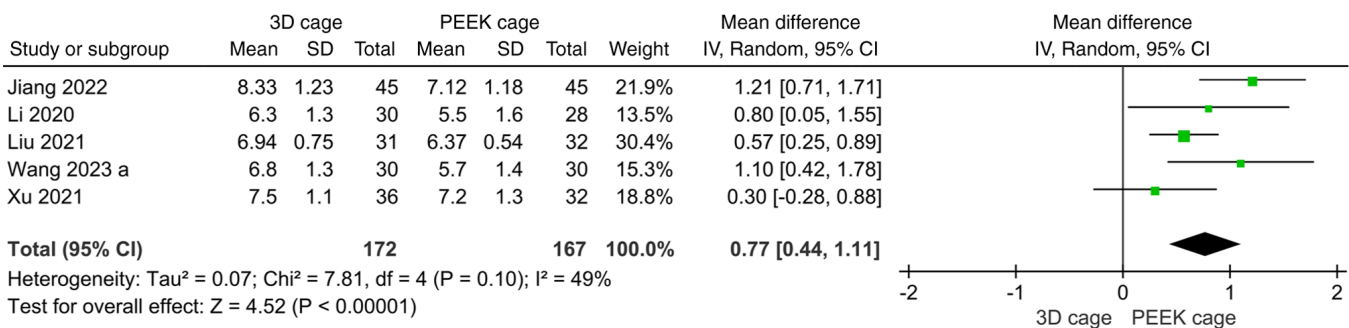


Figure 17. Forest plot after sensitivity analysis of the intervertebral space height. SD, standard deviation; IV, inverse variance; random, random-effects model; df, degrees of freedom; 3D, three-dimensional; PEEK, polyether ether ketone.

vertebral subsidence (34,35). Animal experiments have also shown that 3D cages have better osseointegration characteristics and stability (36,37). The fusion rate is an important indicator

for testing the effects of an operation. There was no significant difference in the fusion rate between the two groups, indicating that the porous titanium fusion cage fabricated via 3D printing

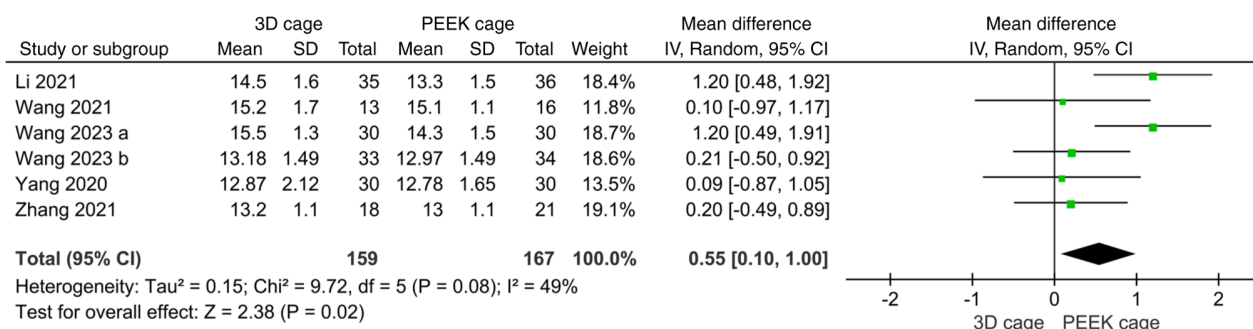


Figure 18. Forest plot after sensitivity analysis of the Japanese Orthopaedic Association Assessment of Treatment. SD, standard deviation; IV, inverse variance; random, random-effects model; df, degrees of freedom; 3D, three-dimensional; PEEK, polyether ether ketone.

in ACDF produced the same fusion results as the conventional PEEK fusion cage. Theoretically, the fusion effect of 3D-printed cages should be higher than that of the PEEK cage, but our results are not consistent. It may be considered that the results of various studies lack long-term efficacy, or as the fusion effect is affected by numerous factors, the material aspect should be considered. The postoperative C2-7 Cobb angle and intervertebral space height in the 3D cage group were greater than those in the PEEK cage group. The C2-7 Cobb angle is an important index for evaluating sagittal imbalance of the cervical spine. Sagittal imbalance of the cervical spine may cause postoperative pain and decrease cervical spine mobility and function (38). Reconstruction of sagittal balance of the cervical spine is important. A decrease in the C2-7 Cobb angle indicates that the cervical curvature becomes straight or even reversed, which may lead to excessive tension and spasm of the muscles of the neck, pain and dysfunction of the neck, and even accelerate the degeneration of the cervical spine, spinal canal stenosis and spinal cord nerve compression. The loss of the C2-7 Cobb angle and intervertebral height in the 3D cage group were significantly smaller than those in the PEEK cage group, indicating that 3D-printed cages had more advantages in maintaining the C2-7 Cobb angle and intervertebral height, which could effectively reduce the loss of cervical curvature and intervertebral height. The upper and lower surfaces of the PEEK cage are dentate features that are in point contact with the upper and lower endplate surfaces and can cause stress concentration. These dentate surfaces have the potential to fall into the vertebral body and reduce the height of the intervertebral gap. The surface of the 3D-printed fusion cage is fabricated according to the curved surface structure of the endplate. The contact area is larger and the stability is better. The complex microstructure of a rough surface is conducive to bone healing (39). Correct handling of the end plates, precise placement angle and the depth of the screws on the plate are key factors in preventing subsidence. When handling endplates with more severe degeneration, care should be taken to not exert too much force to avoid damaging the endplates; furthermore, when placing the interbody fusion cage, it should be entered along the inclined angle of the intervertebral space to prevent the cage from damaging the endplates, leading to postoperative subsidence of the cage (40). However, the studies included in the present meta-analysis did not consider the porosity of the porous titanium fusion device, the treatment of the end plate or the angle of fusion device placement. In terms of postoperative VAS and JOA scores, the 3D-printed cage group was superior to the PEEK cage group, indicating that the application of 3D-printed cage can

reduce postoperative pain and accelerate postoperative functional recovery. The postoperative hospital stay was shorter than that of the PEEK cage group, which also proved this point. This shows that the application of 3D-printed cage can reduce the operation time, intraoperative bleeding and postoperative complications of ACDF, promote recovery of the cervical curvature, improve stability, reduce postoperative pain and accelerate postoperative functional recovery.

The pathogenesis of traumatic cervical spinal cord injury is different from that of cervical spondylosis. Traumatic cervical spinal cord injury refers to damage to the cervical spinal cord caused by an external force that impairs the structural integrity of the cervical vertebrae, thereby involving the cervical spinal cord. Cervical spondylosis is a disease based on degenerative pathological changes in the intervertebral discs. Traumatic cervical spinal cord injury is a serious injury, which frequently leads to impaired sensory, motor and reflex functions of the spinal cord, specifically manifested as quadriplegia and sensory disorders, as well as urinary and fecal dysfunction. The surgery is frequently more difficult, the postoperative recovery process is longer, the recovery of postoperative function is poorer and there are more complications. This is a source of heterogeneity that was expected to affect the present analysis, and thus, it was excluded. Herniated nucleus pulposus (HNP) is one of the common causes of cervical spondylosis. Different parts of protrusion compression are divided into cervical spondylotic radiculopathy and cervical spondylotic myelopathy. Cervical spondylosis caused by HNP was included in the present study, and both nerve root cervical spondylosis and spinal cord cervical spondylosis were also included in this study. The present study focused on cervical spondylosis, but the condition is divided into various types, including cervical spondylotic radiculopathy and myelopathy, the scores of which may vary according to the different etiologic causes of the disease. Toci *et al* (41) used the Short-Form 12 Physical Component and Mental Component scores, VAS arm score and Neck Disability Index to compare improvements in outcome measures reported by patients who underwent ACDF for cervical spondylotic myelopathy or cervical spondylotic radiculopathy, and found that patients with cervical spondylotic myelopathy had better baseline functioning but relatively less postoperative improvement.

The age of the patient is one of the factors that influence the difficulty of intraoperative maneuvers and postoperative outcomes. While the average age of patients in the literature included in the present study ranged from 46-60 years, although the age span was large, statistical comparisons were made in each

of the studies, and there was no statistically significant difference between the age of the control group and the experimental group ($P>0.05$). A total of eight of the studies (17-20,22-24, Xu, unpublished data) had P-values of 0.506, 0.649, 0.813, 0.653, 0.26, 0.765, 0.612 and 0.658, and the remaining four studies (10,16,21,25) did not provide any P-values but all mentioned $P>0.05$ in the text. The effect of patient age on the results needs to be controlled in clinical controlled trials and in the present analysis, patient age in the different studies was a confounding factor, which requires to be controlled. Therefore, it may be assumed that the age factor did not have a significant effect on the present results.

In the present study, it was discovered that using PEEK interbody fusion cages and 3D-printed porous titanium interbody fusion cages in ACDF can reduce postoperative pain and increase functional recovery. The operation time, intraoperative blood loss, postoperative complications and hospitalization time of the 3D-printed porous titanium interbody fusion cage group were less than those of the PEEK interbody fusion cage group, and it also had advantages in maintaining cervical curvature and intervertebral height. It also reduces pain and accelerates postoperative rehabilitation. No significant differences were observed in the rates of intervertebral fusion. Therefore, it is indicated that 3D-printed porous titanium interbody fusion cages are superior to PEEK interbody fusion cages when ACDF is required.

The limitations of the present study were as follows: i) There was only a small proportion of randomized controlled studies included in the present analysis. It is well known that randomized controlled trials are a class of study with the highest quality; however, only four articles were retrieved in line with the search strategy and included in the present study. ii) Currently, research on related issues is focused in China, and there is a lack of research in other countries and ethnic groups; the reason for this is elusive and it is not clear whether the findings are applicable to other countries or ethnic groups. Our group is planning to conduct a collaborative network analysis of related issues in the future. Since there is always heterogeneity in intervention effects among multiple studies from different groups and geographic regions, a random-effects model was always used to account for this. iii) No outcome indicators on sedimentation were reported in the literature. iv) The study population included patients with cervical spondylosis who underwent ACDF using a 3D cage or PEEK cage and there was no differentiation between cervical spondylotic radiculopathy and cervical spondylotic myelopathy; however, the postoperative scores of patients with cervical spondylosis of different etiologies who underwent the same procedure may vary and this is a source of heterogeneity. v) Differences in the number of operated segments among the included studies may have also affected the present results, and different numbers of segments may affect outcome metrics such as operative time and bleeding. Among the studies included, there were three papers (17,21, Xu, unpublished data) with multi-segment ACDF, in which the results of the statistical comparison of the literature regarding the number of surgical segments were $P=0.792$, 0.749 and 0.520 , which were all >0.05 , and there was thus no significant difference. Therefore, a sensitivity analysis was performed for each outcome metric and consistent results were obtained after excluding the studies one by one, which indicates that the present results are reliable. However, heterogeneity cannot be excluded due to differences in study design in the original literature, which is a limitation. Future research

is needed to reduce the influence of confounding factors and more randomized controlled trials with larger sample sizes are needed to obtain more reliable results.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

WJZ and LL were accountable for the design of this study and both performed the statistical analyses. YHG and SLQ made significant contributions to the analysis and interpretation of the data. PFH and YFX drafted the manuscript and critically revised its intellectual content, and contributed significantly to the conceptualization and design of the study. PFH and YFX confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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