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Titanium-coated PEEK Versus Uncoated PEEK Cages in Lumbar Interbody Fusion

A Systematic Review and Meta-analysis of Randomized Controlled Trial

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Study Design: Systematic review and meta-analysis.

Objective: This study was performed to compare the fusion and subsidence rate of titanium-coated polyetheretherketone (Ti-PEEK) versus polyetheretherketone (PEEK) cages after lumbar fusion and to investigate the clinical effect on patient-reported outcomes (PROMs).

Summary of Background Data: Ti-PEEK cages have been developed to combine the advantages of both titanium alloy and PEEK, but whether they are superior to uncoated PEEK cages in bone fusion is still inconclusive.

Methods: PubMed, EMBASE, ISI Web of Science, CENTRAL, and CNKI were searched to identify randomized controlled trials that compared the efficacy of Ti-PEEK and PEEK cages in lumbar fusion. Difference in fusion rate and subsidence rate was indicated by risk ratio and its associated 95% confidence interval (95% confidence interval). Mean difference was calculated for Oswestry Disability Index and visual analogue scale for low back pain. Subgroup analysis was performed by time course after the surgery. The Grading of Recommendations, Assessment, Development and Evaluation approach was used to evaluate the certainty of evidence.

Results: Four randomized controlled trials involving 325 patients (160 patients in Ti-PEEK group and 165 patients in PEEK group) that underwent lumbar fusion were included by our current study. Low to moderate evidence suggested that Ti-PEEK and PEEK cages exhibited equivalent fusion rate and subsidence rate at any follow-up time. Low to moderate evidence suggested that there was no difference in PROMs except for visual analogue scale measured at 6 months (mean difference: −0.57, 95% confidence interval −0.94, −0.21; $P = 0.002$) but the difference was not clinically relevant according to the minimal clinically important difference.

Conclusion: Low to moderate evidence showed that Ti-PEEK and PEEK had equivalent effect in bone fusion and cages subsidence at any follow-up time after lumbar fusion surgeries. Low to moderate evidence showed no clinically important difference in PROMs.

Key Words: titanium-coated PEEK, PEEK, lumbar fusion, systematic review, meta-analysis

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With the growth in the size of the aging population, the incidence of degenerative spinal disorders has increased. The degenerative spinal disorders may result in mechanical back pain, radicular and claudicated symptoms, reduced mobility, which significantly affect patients' quality of life and daily normal function.[1,2] Lumbar interbody fusion has showed excellent clinical outcomes in treating degenerative spinal disorders through stabilizing the painful motion segment, restoring lordosis, correcting deformity, and providing indirect decompression of the neural elements.[2,3]

The interbody cage is the key device in interbody fusion. The ideal interbody cage must be rigid enough to maintain stability, but preferably with a similar elastic modulus to bone to prevent subsidence and stress shielding.[4] Over the past 2 decades, multiple cage materials have been examined, but limitations have been identified for each candidate material. The most common materials used in interbody cages are titanium (Ti and its alloys) and polyetheretherketone (PEEK) due to their good biocompatibility.

As early as the 1940s, Ti and its alloys has been already used in orthopedic surgeries and were subsequently chosen as a component of spinal implants. They were well suited to the bone because of their intrinsic biocompatibility. It could promote the bony fusion by enhancing osseointegration, proliferation of osteoblasts, differentiation of stem cells, cell adhesion, and bone mineralization.[5] Furthermore,

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it has excellent corrosion resistance, low density and toxicity, high fatigue strength, and elastic modulus.[6] Ti6Al4V, one of the most common titanium alloy materials, is the standard medical-grade implant for orthopedic surgeons.[7,8] Despite the favorable fusion rates, Ti is still not an ideal implant for clinical spinal surgery. It has a larger modulus of elasticity than cortical bone, which leads to cage subsidence, causing a series of complications such as cage loosening, local inflammation, rod breakage, and implant failure.[9] PEEK was introduced to the spine word in the 1990s as an alternative cage. Compared with Ti cage, the modulus of elasticity of PEEK cage is closer to that of cortical bone. It provides the ability for minimizing stress shielding and preventing subsidence.[10] Furthermore, it allows for postoperative imaging to assess the extent of bone fusion, because of its radiolucent property.[11] However, PEEK has chemically inert face, which may limit its potential to promote protein absorption, cell adhesion, and bone fusion.[12] To combine the advantages of Ti and PEEK, Cheol and colleagues created a titanium-coated polyetheretherketone (Ti-PEEK) composite by coating the surface of PEEK with Ti.[13]

Although several studies have compared the clinical effectiveness of PEEK and Ti-PEEK cages in lumbar fusion surgeries but no consensus has been achieved. As far as we know, no meta-analysis has been carried out to assess the differences between PEEK and Ti-PEEK cages. Therefore, we conducted this systematic review and meta-analysis with all available literature aiming to provide a comprehensive and up-to-date comparison of uncoated PEEK and Ti-PEEK cages in lumbar fusion surgery, with a focus on the fusion and subsidence rate, and the clinical effect on patient-reported outcomes (PROMs).

METHODS

This systematic review and meta-analysis was conducted in accordance with the the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[14]

Literature Search

A comprehensive literature search was conducted using 5 online databases including PubMed, EMBASE, ISI Web of Science, CENTRAL, and CNKI to retrieve eligible studies that published before December 2020. No restriction on language was imposed for literature search. The following search strings were used for English online databases: (Ti-PEEK or Titanium) and (PEEK) and [spine or lumbar fusion or posterior lumbar interbody fusion (PLIF) or transforaminal lumbar interbody fusion (TLIF)] and [randomized controlled trial (RCT) or random]. For CNKI, we used "PEEK" and "Titanium" and "Yao Zhui Rong He". The reference lists of related systematic reviews and meta-analyses[4,15,16] were also checked for additional eligible records. Before the submission of our study, the literature search process was repeated to obtain potentially available studies that published after the initial literature search.

Eligibility Criteria

The inclusion criteria were established following the PICOS (Participants, Intervention, Control, Outcome, Study design) principle: (P) patients presenting with degenerative spondylolisthesis, degenerative scoliosis, lumbar spinal canal stenosis, lumbar radiculopathy, lumbar herniation, or isthmic spondylolisthesis that scheduled to undergo standard open PLIF or TLIF with artificial interbody cage were included in our study; (I) patients in the Ti-PEEK groups were treated with Ti-PEEK cages, which have identical dimensions and angulation with noncoated PEEK cages; (C) patients in the control groups were treated with PEEK cages; (O) the primary outcome was bone fusion rate and cage subsidence rate, secondary outcomes included PROMs such as Oswestry Disability Index (ODI) and visual analogue scale (VAS) for low back pain; (S) only prospective RCTs were considered by our study.

Studies met the following exclusion criteria were excluded: (i) case reports and case series; (ii) reviews, editorials and commentary articles; (iii) <10 patients in each study arm or the follow-up period was <12 months. In case of conference abstracts the corresponding authors were contacted through e-mail, and the records would be excluded if no raw data were available. If multiple studies with overlapping data were identified, only the most comprehensive one was included by our study.

Data Extraction

Two reviewers screened each eligible article independently and were blinded to the findings of the other reviewer. The data from each individual study was collected using a predetermined data collection sheet which included surname of the first author, year of publication, study design, sample size, country of origin, mean age of participants, mean body mass index (BMI) of participants, clinical outcomes, adverse events, follow-up period, type of surgical procedure, type of bone graft, type of interbody cages, surgical indications, operated levels, definition of bone fusion rate and cage subsidence rate, modality used for fusion, and subsidence assessment. Any discordance between the 2 reviewers was resolved through discussion until a mutual consensus was reached. Otherwise, the third reviewer was consulted for his opinion.

Risk of Bias Assessment

The Cochrane Collaboration's tool based on 7 items (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias) was utilized to assess the risk of bias in the included studies. The risk of bias assessment was finished by 2 independent reviewers with their results being compared afterwards. Disagreements regarding the risk of bias assessment were settled by discussion and consensus between reviewers.

Quantitative Synthesis

For bone fusion rate and cage subsidence rate after the lumbar fusion, the risk ratio (RR) and its associated 95% confidence interval (95% CI) were calculated and synthesized using the software RevMan 5.3 (Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). The mean difference (MD) was calculated and combined for continuous variables using the same method. The χ^2 test and the Higgins I^2 test were used to assess the between-study inconsistency ($P > 0.1$ and $I^2 < 50\%$ indicated nonsignificant heterogeneity).[17] In our current study, we pooled the data from each individual study using the random-effect model regardless of the magnitude of intrastudy heterogeneity due to the presence of anticipated heterogeneity.[18,19] Subgroup analysis by time course (3, 6, and 12 mo) was performed to compare the efficacy of Ti-PEEK with PEEK cages at different follow-up time points. Begg rank correlation test and Egger linear regression test were used to detect the publication bias using Stata software version 12.0 whether the number of included studies was > 5 (Stata Corp LP, USA).[20]

To assess whether the statistically significant changes in PROMs were clinically relevant, the minimal clinically important difference (MCID) for each PROM was used to interpret the results of meta-analysis. MCIDs have been previously established for VAS (MCID = 1.2) and ODI (MCID = 12.8).[21]

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Approach

GRADE approach was adopted to assess the certainty of evidence for each outcome.[22] Using this approach, evidence from included studies was initially graded as "high quality" but could be downgraded to "moderate quality", "low quality" or "very low quality" depending on the presence and seriousness of 5 categories of limitations: risk of bias, indirectness, inconsistency, imprecision, and publication bias. A summary of findings table was generated to show and explain the final results. Two reviewers who performed the risk of bias assessment were responsible for the GRADE approach.

RESULTS

Literature Search

The flow of literature search and screen was illustrated in Figure 1. A total of 64 records were identified through the initial literature search, including 8 from

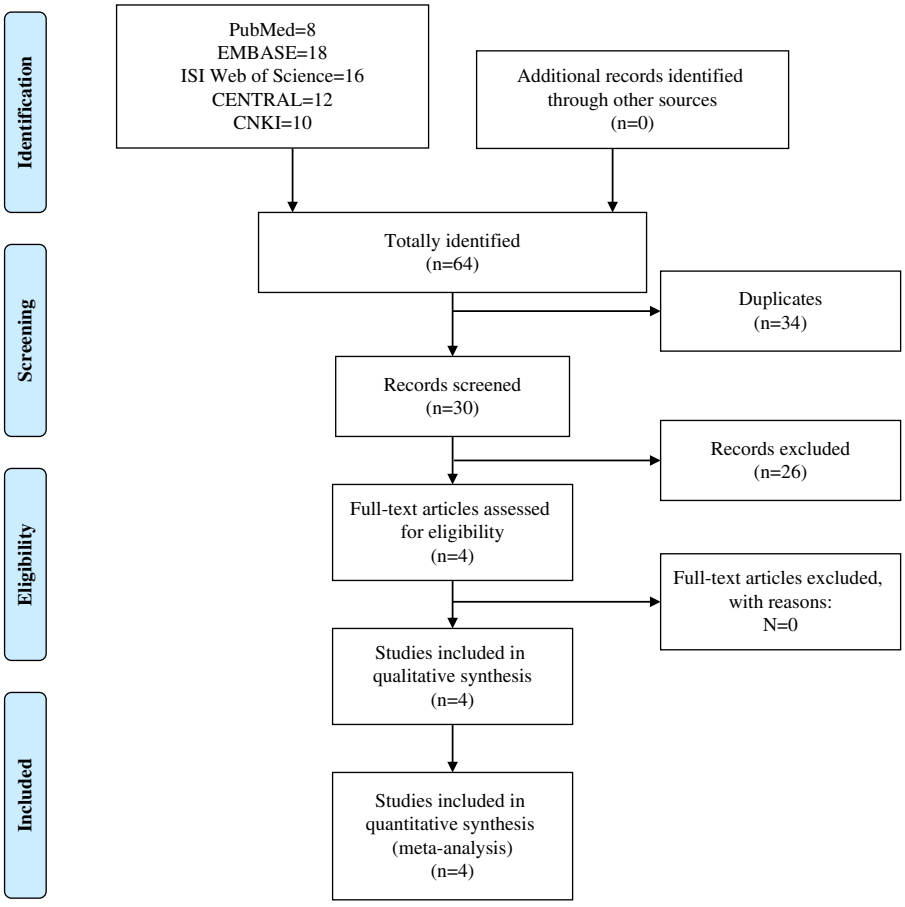

FIGURE 1. Flow chart of literature search and screen. full color online

TABLE 1. Main Baseline Characteristics of Included Studies

Study	Country	Study Design	Sample Size (Ti-PEEK/PEEK)	Mean age (Ti-PEEK/PEEK)	Mean BMI (Ti-PEEK/PEEK)	Clinical Outcomes	Adverse Events	Follow-up
Hasegawaet al[23]	Japan	Multicenter prospective RCT	69/80	67.4/67.0	24.3/23.7	JOABEPQ, ODI	Reported	12 mo
Rickert et al[24]	Germany	Single-center prospective RCT	20/20	67.7/68.3	27.7/28.5	ODI, EQ-5D, VAS	Reported	12 mo
Schnake et al[25]	Germany	Single-center prospective RCT	27/28	50.6/52.9	27.1/28.8	ODI, EQ-5D, VAS	Reported	24 mo
Willems et al[26]	Belgium	Single-center prospective RCT	44/37	50.0/51.5	NR	ODI, VAS, SF-36	Reported	12 mo

BMI indicates body mass index; EQ-5D, Euro-Qol-5D; JOABEPQ, Japanese Orthopaedic Association Back Pain Evaluation Questionnaire; NR, not reported; ODI, Oswestry Disability Index; PEEK, polyetheretherketone; RCT, randomized controlled trial; SF-36, 36-Item Short Form Survey; Ti-PEEK, Titanium-coated PEEK; VAS, visual analogue scale.

PubMed, 16 from ISI Web of Science, 18 from EMBASE, 12 from CENTRAL, and 10 from CNKI. Almost half of the identified records were duplicates, after the removal of these 34 duplicated records, the remaining 30 studies were screened with titles and abstracts. Another 26 studies were further excluded as they were not related with Ti-PEEK cages in lumbar fusion surgeries. Finally, 4 studies [23–26] were deemed eligible to be included in our analysis, all of which were based on a RCT design comparing the effectiveness of Ti-PEEK and PEEK in spine surgeries.

Main Characteristics

Four RCTs involving 325 patients (160 patients in Ti-PEEK group and 165 patients in PEEK group) that underwent PLIF or TLIF surgeries were included by our current study. All the studies were written in English and got published between 2017 and 2020. Three studies[24–26] were carried out in a single center whereas one study[23] was based on a multicenter design. Studies were performed in Japan,[23] Germany,[24,25] and Belgium,[26] respectively, with a sample size ranging from 40 to 149. The main baseline characteristics of included studies were summarized in Table 1, all the studies reported similarity in baseline information, including mean age, BMI and gender distribution. Adverse events after the surgeries were recorded by all studies, with a follow-up period ranging from 12 to 24 months. PLIF was performed in 3 studies[23,25,26] for 260 patients, TLIF was performed in 2 studies[23,24] for 65 patients. To fill the interbody cages, 3 of our included studies used local bone graft solely, whereas Rickert et al[24] used both local bone chips and bone substitute. Detailed information of types of interbody cages, surgical indication, and lumbar levels for each included study was presented in Table 2.

Risk of Bias Assessment

The results of risk of bias assessment were shown in Figures 2 and 3. Three [23,24,26] out of 4 included studies reported the method for random sequence generation, only half of the studies [23,26] reported information of allocation concealment. In terms of blinding of participants and personnel, 3 studies [23,24,26] were judged to be low risk of bias. Blinding of outcome assessment was not mentioned by Rickert's study.[24] Rickert's study was also judged to have high risk of attrition bias as the dropout rate in PEEK group was 25%. No other bias was detected among our included studies.

Meta-analyses Results

Fusion Rate

The bony fusion status was evaluated by all included studies, mostly at 6 months and 12 months after the surgery but as early as 2 months in Hasegawa's study.[23] However, the definition of fusion was not uniform across included studies, although all the included studies took the presence or absence of bony bridging into consideration (the Bridwell's criteria). It should be noted that all included RCTs used thin-slice 3D computed tomography to assess the bony fusion status, 3 RCTs [23–25] used functional

TABLE 2. Detailed Information of Surgical Procedure for Each Included Study

Study	Surgical Procedure (Ti-PEEK/PEEK)	Bone Graft	Type of Cages	Surgical Indication (Ti-PEEK/PEEK)	Lumbar Level (Ti-PEEK/PEEK)
Hasegawa et al[23]	PLIF: 58/66 TLIF: 11/14	Local bone	NR	Degenerative spondylolisthesis: 28/34 Degenerative scoliosis: 1/0 Lumbar spinal canal stenosis: 36/48 Lumbar radiculopathy: 1/4 Lumbar herniation: 10/6 Isthmic spondylolisthesis: 4/5	L2–L3: 3/1 L3–L4: 8/7 L4–L5: 41/52 L5–S1: 17/20
Rickert et al[24]	TLIF: 20/20	Local bone+bone substitutes	Ti-PEEK: MectaLIF Ti-PEEK, Medacta International SA PEEK: MectaLIF PEEK, Medacta International SA	Degenerative disk disease: 9/10 Spinal stenosis: 7/6 Isthmic/low dysplastic spondylolisthesis: 3/2 Degenerative spondylolisthesis: 1/2	L2–L3: 1/1 L3–L4: 9/10 L4–L5: 14/15
Schnake et al[25]	PLIF: 27/28	Local bone	Ti-PEEK: coated Wave, Medtronic PEEK: Wave, Medtronic	Advanced degenerative disk disease: NR/NR Lumbar spinal canal stenosis: NR/NR Degenerative spondylolisthesis: NR/NR Postnucleotomy syndrome: NR/NR	L2–L3: 0/2 L3–L4: 1/4 L4–L5: 11/18 L5–S1: 17/12
Willems et al[26]	PLIF: 44/37	Local bone	Ti-PEEK: TSC, Orthobion PEEK: reCreo, Orthobion	Degenerative disk disease: NR/NR Spondylolisthesis: NR/NR Spinal canal stenosis: NR/NR	T6–T7: 1/1 L2–L3: 0/1 L3–L4: 4/2 L4–L5: 18/13 L5–S1: 21/20

NR indicates not reported; PEEK, polyetheretherketone; PLIF, posterior lumbar interbody fusion; Ti-PEEK, titanium-coated PEEK; TLIF, transforaminal lumbar interbody fusion.

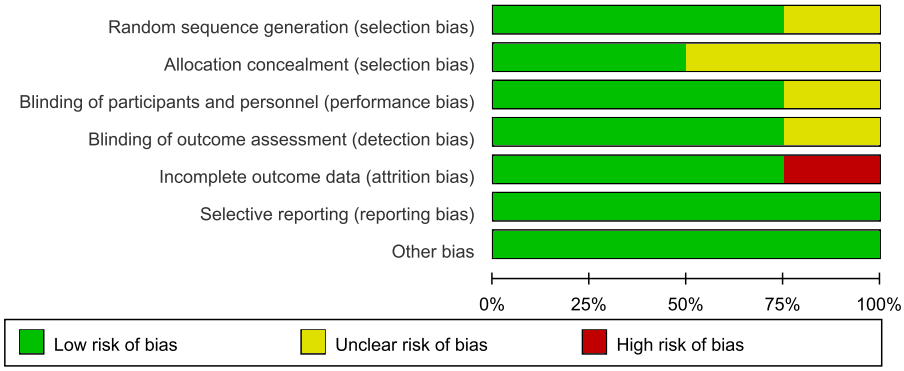

FIGURE 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies. full color online

x-rays in addition to that. Schnake and coworker further considered the segmental instability when establishing their own criteria for successful bony fusion.[25] Hasegawa and colleagues evaluated the fusion status at both coronal and sagittal planes, thereby making the criteria for successful fusion even more rigorous. The definition of fusion and subsidence rates used in each study, and the main results of each study were summarized in Table 3.

By 6 months after the surgery, the range of fusion rates was 36.2%–100.0% in Ti-PEEK group and 20.0%–100.0% in the PEEK group. By 12 months after the surgery, the fusion rates ranged from 42.0% to 100.0% in Ti-PEEK group and from 41.3% to 100.0% in PEEK group. Combined RR using random-effect model suggested no difference in fusion rates between Ti-PEEK group and PEEK group at either 6 months (RR: 1.07, 95% CI 0.85, 1.35; $P=0.56$; $I^2=84\%$) or 12 months (RR: 0.98, 95% CI 0.93, 1.04; $P=0.58$; $I^2=0\%$), as shown in Figure 4.

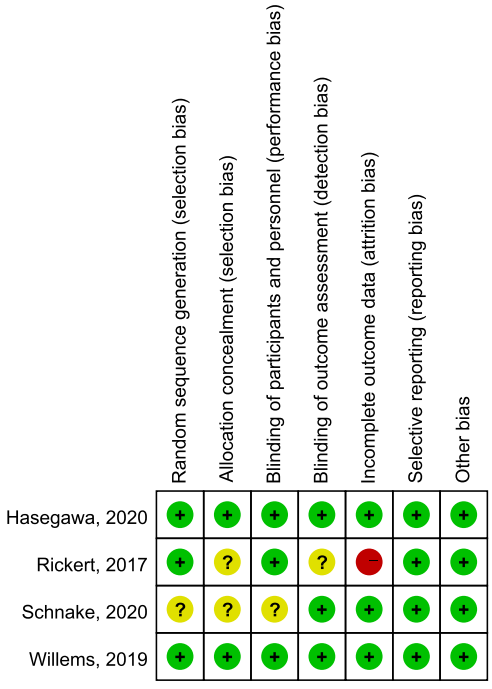

FIGURE 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study. full color online

Subsidence Rate

Interbody subsidence was measured by 3 included studies,[23–25] the definition of subsidence was summarized in Table 3. The combined RR showed no difference of subsidence rate between Ti-PEEK group and PEEK group at 6 months (RR: 1.01, 95% CI 0.41, 2.47; $P=0.99$) and 12 months (RR: 1.05, 95% CI 0.50, 2.17; $P=0.90$; $I^2=0\%$) after surgery (Fig. 5).

ODI

ODI is a commonly used scale to assess the disability associated with low back pain (lower values indicated better condition), and it was reported by all the included studies. Significant improvement in ODI score was noted in both groups in each included study, the improvement was present at any postoperative time point. The combined ODI showed no difference between Ti-PEEK and PEEK at any follow-up time period: 3 months (MD: −3.56, 95% CI −8.05, 0.93; $P=1.23$), 6 months (MD: −1.10, 95% CI −6.21, 4.02; $P=0.67$), and 12 months (MD: 1.78; 95% CI −2.82, 6.38; $P=0.45$), as shown in Figure 6.

VAS

VAS for back pain was recorded by 3 included studies,[24–26] all of them used the 0–10 points scale and the follow-up lasted for at least 12 months. Immediate improvement in pain intensity was observed in both groups in each study, and the improvement was still present till the end of follow-up. The pooled VAS suggested no better effect of Ti-PEEK than uncoated PEEK in pain relief at 3 months (MD: −0.04, 95% CI −1.03, 0.94; $P=0.93$) and 12 months (0.18, 95% CI −0.76, 1.13; $P=0.70$). But Ti-PEEK was associated with significantly lower pain intensity than PEEK at postoperative 6 months (−0.57, 95% CI −0.94, −0.21; $P=0.002$), which was further supported by low intrastudy inconsistency ($I^2=0\%$), but the difference did not reach a MCID of 1.2 points (Fig. 7).

TABLE 3. Definition of Fusion and Subsidence Rates Used in Each Included Study, and The Main Results of Each Study

Study	Definition of Fusion	Definition of Subsidence	Modality	Blinded Evaluation	Fusion Rate (Ti-PEEK/PEEK)	Subsidence Rate (Ti-PEEK/PEEK)
Hasegawa et al[23]	Fusion graded according to the modified Bridwell classification (I, II, and III), complete interbody bone fusion as an angular motion of <5 degrees at the fusion level and the presence of upper and lower bone fusions, whereby both coronal and sagittal CT slices were evaluated as grade I	Sinking of the cage (subsided > 1 mm) on CT when compared with its position soon after the surgery	Thin-slice 3D-CT and functional x-rays	Yes	6 mo: 36.2%/20.0% 12 mo: 42.0%/41.3%	6 mo: 11.9%/11.8% 12 mo: 15.6%/14.9%
Rickert et al[24]	Fusion graded according to the modified Bridwell classification, which included presence or absence of bony bridging	Loss of disk space height of 1 > mm with a visible fracture of the vertebral body endplate	Thin-slice 3D-CT and functional x-rays	NR	12 mo: 91.7%/91.7%	12 mo: 0.0%/0.0%
Schnake et al[25]	The criteria established by McAfee and Abbushi were used, which included presence or absence of bony bridging and segmental instability (in the flexion–extension images ˃5 deg)	Sinking of the cage (subsided > 3 mm) on CT	Thin-slice 3D-CT and functional x-rays	Yes	6 mo: 100.0%/100.0% 12 mo: 100.0%/100.0%	12 mo: 3.6%/3.6%
Willems et al[26]	Definite fusion was defined as presence of at least 2 bridging bony trabeculae passing from one vertebral endplate to the other in both the sagittal and coronal planes; probable fusion was defined as at least 1 bridging bony trabecula passing from one vertebral endplate to the other in the sagittal or coronal plane	NR	Thin-slice 3D-CT	Yes	6 mo: 94.2%/91.2% 12 mo: 96.9%/100.0%	NR

CT indicates computed tomography; NR, not reported; PEEK, polyetheretherketone; Ti-PEEK, titanium-coated PEEK.

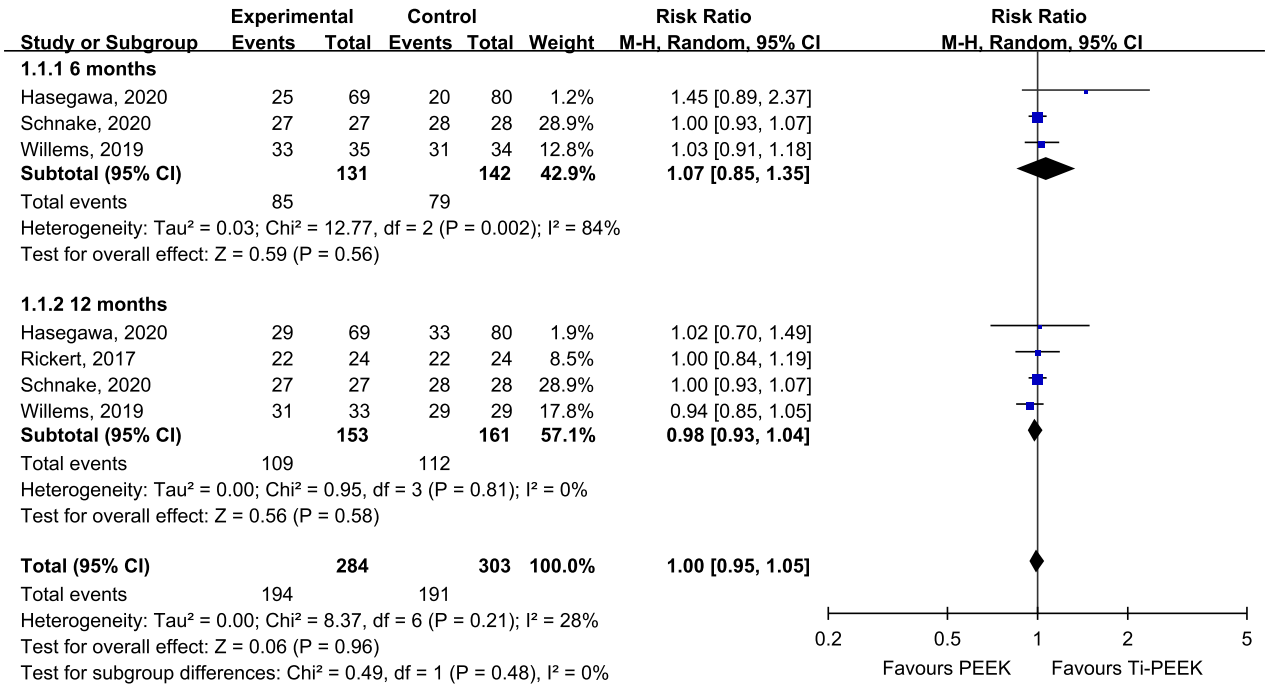

FIGURE 4. Forest plot of fusion rate: subgroup by follow-up time (6 mo and 12 mo). CI indicates confidence interval; PEEK, polyetheretherketone; Ti-PEEK, titanium-coated polyetheretherketone. full color online

Other Clinical Outcomes

In addition to ODI, the Japanese Orthopedic Association Back Pain Evaluation Questionnaire (JOABPEQ), which involves several domains (pain-related disorders, lumbar spine dysfunction, gait disturbance, social life dysfunction, and psychological disorders) was also used by Hasegawa et al.[23] They found out that all domains were improved 12 months after surgery compared with the preoperative status, but no differences between PEEK and Ti-PEEK were observed. Willems et al[26] asked the enrolled patients to fill out the SF-36 survey 12 months after the surgery, and they found no statistically significant differences between PEEK and Ti-PEEK at each moment in time.

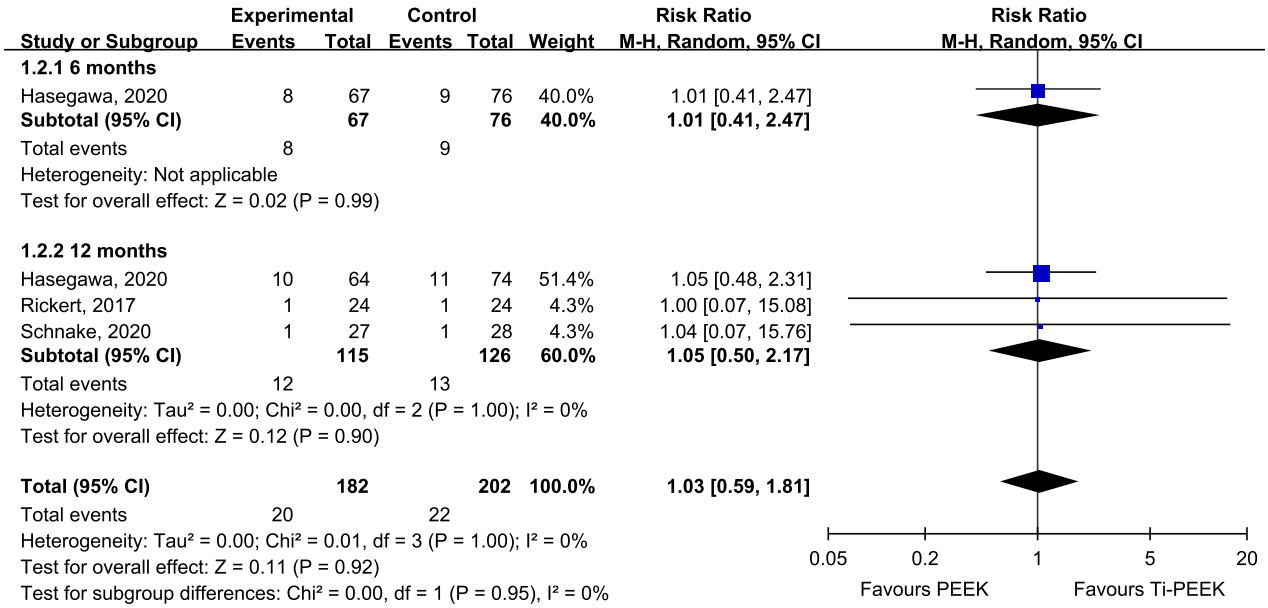

FIGURE 5. Forest plot of subsidence rate: subgroup by follow-up time (6 mo and 12 mo). CI indicates confidence interval; PEEK, polyetheretherketone; Ti-PEEK, titanium-coated polyetheretherketone. full color online

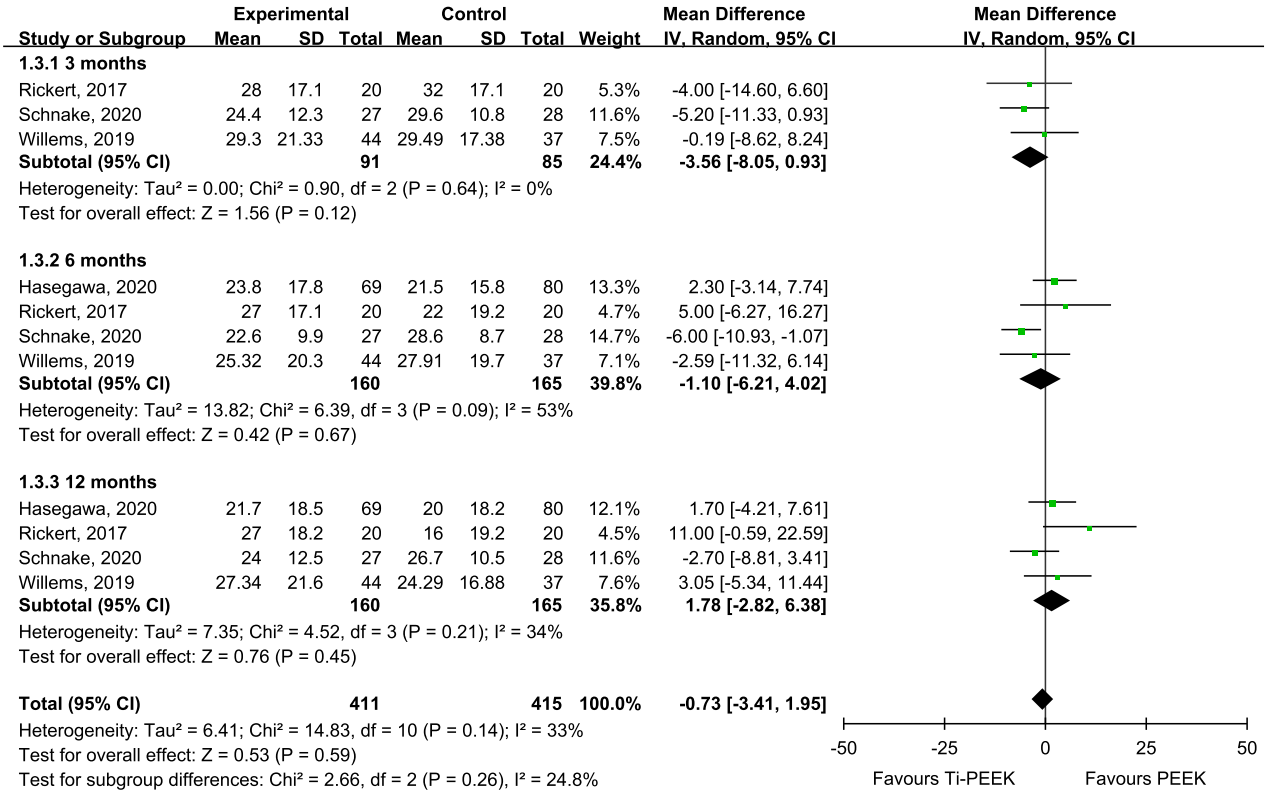

FIGURE 6. Forest plot of Oswestry Disability Index: subgroup by follow-up time (3, 6, and 12 mo). CI indicates confidence interval; PEEK, polyetheretherketone; Ti-PEEK, titanium-coated polyetheretherketone. full color online

Adverse Events

Hasegawa et al[23] reported 2 adverse events in the Ti-PEEK group (1 patient experienced screw mal-positioning and 1 experienced a grafted bone back out) and 1 adverse event in the PEEK group (cerebral infarction). Rickert et al [24] reported a slightly higher incidence of adverse event in the Ti-PEEK group than the PEEK group, but all the complications were related to procedure rather than the implants. In the remaining 2 included RCTs,[25,26] no postoperative complications occurred.

GRADE Approach

The evidence profile of different outcomes using the GRADE was summarized in Table 4. As we only included studies with RCT design, an initial rating of "high" could be assigned to all the outcomes that could be subsequently downgraded based on the presence and seriousness of the following 5 factors: risk of bias, inconsistency, imprecision, indirectness, and publication bias. In our current study, the certainty of evidence for all the outcomes was downgraded for at least 1 level due to imprecision (the total number of participants for each outcome was <400), some outcomes were downgraded for 2 levels due to significant intrastudy inconsistency.

DISCUSSION

The clinical differences between Ti-PEEK and uncoated PEEK cages in lumbar fusion surgeries have been studied, but achieving inconsistent results. To avoid the shortage of insufficient sample size in individual studies, this systematic review and meta-analysis was conducted. In this meta-analysis, 4 RCTs with a total of 160 patients in Ti-PEEK group and 165 patients in PEEK group were included. Our data did not reveal a significant difference in bony fusion rates and cage subsidence rates between PEEK and Ti-PEEK at any follow-up time point, which contradicted previous meta-analyses.[4,15,16] But it should be noted, in previously published meta-analyses, Ti cages and Ti-PEEK cages were treated as the same material and compared with PEEK cages in lumbar fusion surgeries, which could be strategically wrong.

The first RCT to compare PEEK cages and Ti-PEEK cages in lumbar fusion was conducted by Rickert et al,[24] they reported no difference in the bone fusion rate and cage subsidence rate between PEEK cages and Ti-PEEK cages, which was subsequently confirmed by Willems' and Schnake's study.[25,26] But a recent study by Hasegawa and coworkers showed different results, in which stricter criteria for bony fusion was applied and patients were followed for a longer period. We speculated that the inconsistencies in these studies may be explained by several factors. Firstly, all these 4 RCTs only enrolled dozens of patients not hundreds, which might lack the statistical power to detect the difference between PEEK and Ti-PEEK cages in lumbar fusion. Second, all the surgeons filled the intervertebral disk space with an

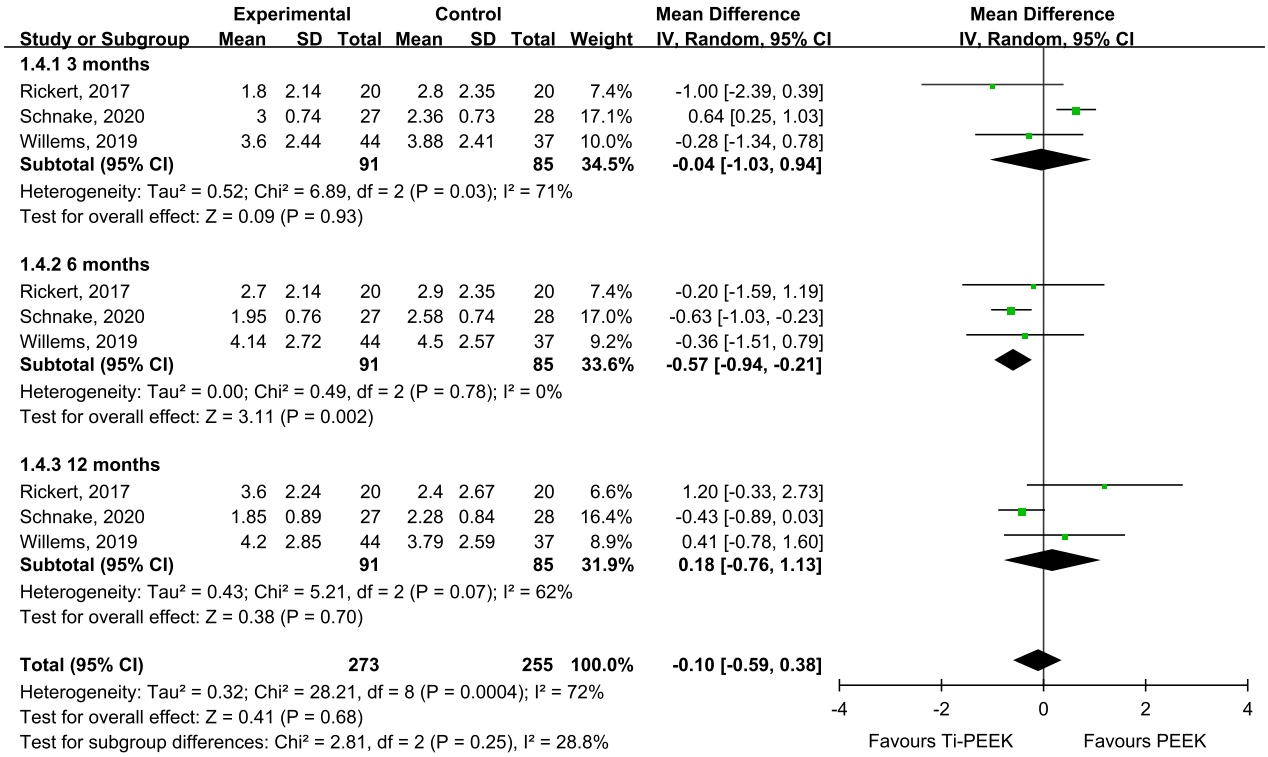

FIGURE 7. Forest plot of visual analogue scale: subgroup by follow-up time (3, 6, and 12 mo). CI indicates confidence interval; PEEK, polyetheretherketone; Ti-PEEK, titanium-coated polyetheretherketone. full color online

autograft or allograft before inserting the cage, which will enhance the bony fusion. But not all of our included studies indicated whether and how they packed the disk space during the surgery. Therefore, it was surprisingly difficult to detect the subtle changes between the 2 groups. Third, it is well known that various factors will affect the bony fusion after lumbar fusion surgery, such as endplate preparation, contact area, cage shape, and systemic illness.[16,27,28] The ignorance of these factors in the above studies might also lead to inconsistencies in the results. In terms of cages subsidence rate, our combined data suggested that Ti-PEEK cages was not associated with higher subsidence rate than uncoated PEEK cages. This is reasonable as Ti was only coated on the surface of PEEK cages, the elastic modulus of both cages remained almost the same.

In clinical practice, the primary goal of an interbody fusion surgery is to alleviate PROMs and maintain good clinical function no matter which kind of cage is used during the lumbar fusion surgery. VAS and ODI are commonly used patient-reported questionnaires for clinical outcomes assessment. Our pooled results revealed that Ti-PEEK cages were associated with significantly lower leg pain intensity than PEEK cages at postoperative 6 months, but the difference did not reach a MCID of 1.2 points. At the end of 12 months' follow-up, no difference was observed between the 2 groups. The combined ODI also suggested no difference between PEEK and Ti-PEEK at any follow-up time point.

Postoperative complications, including screw malpositioning and grafted bone back out, were related to the surgery procedure rather than the implants in this study. As the surgical technique to place both PEEK and Ti-PEEK cage were similar, Ti-PEEK cages used in our included studies had identical dimensions and angulation with noncoated PEEK cages, the differences of adverse events between two groups were not expected to be significant. Furthermore, baseline demographic information (mean age, BMI, and gender distribution), surgical indication, and lumbar fusion levels of both groups were similar. The baseline similarities explained why there was no difference in adverse events between the 2 groups.

Several limitations should not be ignored when interpreting the results of our study. Firstly, the strength of this study is limited by the relatively small sample size of each included RCT. Only 4 high-quality RCTs were included in our meta-analysis. And all of these studies enrolled only dozens of participants, instead of hundreds. The follow-up period in most of the studies ranged from 6 to 12 months, which may underestimate the incidence of clinical and radiologic outcomes. To improve the sensitivity of detecting subtle difference between PEEK and Ti-PEEK cages, RCTs with larger sample size and longer follow-up period are encouraged. Second, different types of PEEK and Ti-PEEK implants were selected for individual RCT. In addition, endplate preparation, contact area, and cage shape may also confound the results. Third, the interbody fusion technique and underlying clinical

TABLE 4. Summary of Findings From RCTs Comparing The Effect of Ti-PEEK and PEEK in Lumbar Fusions

Outcome	No.Studies (Participants)	ROB	Indirectness	Inconsistency	Imprecision	Publication Bias	Pooled Effect	I^2	GRADE
Fusion rate									
6 mo	3 (273)	Not serious	Not serious	Serious*	Serious†	Undetected	RR: 1.07 (0.85, 1.35)	84%	Low
12 mo	4 (314)	Not serious	Not serious	Not serious	Serious†	Undetected	RR: 0.98 (0.93, 1.04)	0%	Moderate
Subsidence rate									
6 mo	1 (143)	Not serious	Not serious	Undetected	Serious†	Undetected	RR: 1.01 (0.41, 2.47)	NA	Moderate
12 mo	3 (241)	Not serious	Not serious	Not serious	Serious†	Undetected	RR: 1.05 (0.50, 2.17)	0%	Moderate
ODI									
3 mo	3 (176)	Not serious	Not serious	Not serious	Serious†	Undetected	MD: −3.56 (−8.05, 0.93)	0%	Moderate
6 mo	4 (325)	Not serious	Not serious	Serious*	Serious†	Undetected	MD: −1.10 (−6.21, 4.02)	53%	Low
12 mo	4 (325)	Not serious	Not serious	Not serious	Serious†	Undetected	MD: 1.78 (−2.82, 6.38)	34%	Moderate
VAS									
3 mo	3 (176)	Not serious	Not serious	Serious*	Serious†	Undetected	MD: −0.04 (−1.03, 0.94)	71%	Low
6 mo	3 (176)	Not serious	Not serious	Not serious	Serious†	Undetected	MD: −0.57 (−0.94, −0.21)	0%	Moderate
12 mo	3 (176)	Not serious	Not serious	Serious*	Serious†	Undetected	MD: 0.18 (−0.76, 1.13)	62%	Low

GRADE: Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
*Downgraded as the intrastudy inconsistency was significant ($I^2 > 50\%$).
†Downgraded for continuous variables if the sample size was <400.
GRADE indicates Grading of Recommendations, Assessment, Development and Evaluation; MD, mean difference; NA, not applicable; ODI, Oswestry Disability Index; PEEK, polyetheretherketone; RCT, randomized controlled trial; ROB, risk of bias; RR: ratio risk; Ti-PEEK, titanium-coated PEEK.

conditions may be inconsistent among four studies. And the majority of included RCTs were performed among Whites, whereas only 1 study was conducted among the Asian population. Therefore, more high-quality studies are needed to verify our result. Last, we performed a GRADE approach to assess the certainty of evidence. In our current study, the certainty of evidence for all the outcomes was downgraded for at least 1 level due to imprecision (the total number of participants for each outcome was <400), some outcomes were even downgraded for 2 levels due to significant intrastudy inconsistency. Therefore, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

In conclusion, low to moderate evidence showed that Ti-PEEK and PEEK had equivalent effect in bone fusion and cages subsidence at any follow-up time after lumbar fusion surgeries. Low to moderate evidence showed no clinically important difference in PROMs. In the future, RCTs with larger sample size and longer follow-up are required to verify these findings.

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