Nano-hydroxyapatite/Polyamide 66 cage in anterior cervical corpectomy and fusion: a comprehensive systematic review and meta-analysis

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Abstract. – OBJECTIVE: This study aimed to conduct a meta-analysis to compare the effectiveness and safety between titanium mesh cage (TMC) and nano-hydroxyapatite/polyamide 66 cage (n-HA/PA66) in the surgical treatment of cervical spondylotic myelopathy (CSM) through anterior cervical corpectomy and fusion (ACCF).

MATERIALS AND METHODS: We implemented a comprehensive search strategy across multiple databases, including Wanfang, China Knowledge Network, China Biomedical Literature Database, Wipu, PubMed, Cochran, Embase, and Web of Science. To ensure a thorough examination of available literature, the databases were searched from their inception to January 2023. Two independent researchers evaluated the quality of the included studies by using established criteria. We used RevMan 5.4 (Review Manager Web, The Cochrane Collaboration, Copenhagen, Denmark) to facilitate data extraction and analysis.

RESULTS: This analysis included seven controlled clinical studies. The meta-analysis results showed no statistically significant differences between the two groups in terms of operating time, intraoperative bleeding, preoperative Japanese Orthopedic Association (JOA) score, preoperative visual analog scale (VAS) score, preoperative and final follow-up C2–7 Cobb angles, and intervertebral fusion rate ($p > 0.05$). However, a significant difference was observed between the two groups in terms of the final follow-up JOA [MD = 0.77, 95% CI (0.58, 0.97), $p < 0.00001$], VAS [MD = -0.50, 95% CI (-0.71, -0.30), $p < 0.00001$], and sedimentation rate [RR = 0.30, 95% CI (0.18, 0.48), $p < 0.00001$].

CONCLUSIONS: The use of n-HA/PA66 in ACCF for treating CSM is safe and effective treatment with positive clinical efficacy. In addition, n-HA/PA66 has both effective clinical efficacy and significantly lower fusion settling rates compared to TMC.

Key Words:
  Nano-hydroxyapatite/polyamide 66 fusion cage, Systematic review and meta-analysis, Titanium mesh cage, Anterior cervical corpectomy, Fusion.

Introduction

Cervical spondylotic myopathy (CSM) is the predominant etiology for non-traumatic impairment of spinal cord function, with an incidence ranging from 12% to 30%. It is typically caused by prolonged cervical loading, cervical spine degeneration, and other factors, leading to cervical spinal canal constriction, resulting in the spinal cord and associated nerve compression. CSM presents with severe clinical symptoms and can result in hemiparesis, paraplegia, and even quadriplegia, which significantly impact the quality of life and can be potentially life-threatening. Therefore, prompt surgical intervention is recommended after diagnosis[1,2]. Anterior cervical corpectomy and fusion (ACCF) is widely recognized as the most frequently used surgical procedure for treating CSM because it is performed through an anterior cervical approach, which directly exposes the compressed lesion, completely decompresses the spinal canal, relieves spinal nerve compression, and fully restores spinal cord and nerve function. ACCF has been widely applied in clinical practice due to significant postoperative restoration of the spinal cord and neurological function and effective restoration of cervical curvature[3]. As technology continues to advance, cervical spine reconstruction after laminectomy has become of increasing interest. Thus, implant materials and fusion devices have been developed for cervical spine reconstruction, with satisfactory results. Initially, autologous bone (iliac or fibula) grafts were used, which were recognized as the gold standard for bone grafting[4]. However, complications associated with autogenous bone grafts, such as infection, hematoma, and pain, cannot be ignored. Compared to autogenous bone grafts, the use of allograft bone grafts reduces surgical trauma, decreases operative time, and

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effectively minimizes complications; however, it increases graft subsidence rate and carries risks of immune rejection reactions and infectious disease transmission[5]. Recently, a titanium mesh cage (TMC), which is a metallic fusion device, has been widely used for cervical spine reconstruction following corpectomy. Particularly, when filled with autogenous bone[6], TMC has many advantages, such as fewer complications in the donor area, shorter operative time, and higher fusion rates at 97-100%[7,8]. However, previous studies[9,10] have reported some disadvantages of TMC, including high subsidence rates and stress shielding. However, recent research in spinal vertebral reconstruction has focused on non-metallic materials as alternatives to traditional metallic materials to address these limitations. Since nano-hydroxyapatite/polyamide 66 cage (n-HA/PA66) was clinically used in 2005, it has gradually gained satisfactory clinical outcomes in the short term[11]. Indeed, n-HA/PA66 is a biomimetic composite material formed through the combination of hydroxyapatite and polyamide 66, and it effectively maintains cervical height and alignment. It has advantages, such as low subsidence and high fusion rates, and it can meet vertebral support strength while minimizing stress shielding effects[12].

The safety and efficacy of n-HA/PA66 in treating CSM in ACCF have been reported in some studies but are limited by small sample size and weak evidence strength. Thus, a meta-analysis was proposed as a quantitative method to combine data from multiple studies on the safety and efficacy of n-HA/PA66 in CSM treatment, thereby increasing sample size and generating higher evidence quality. However, further improvement is necessary in conducting this meta-analysis. Therefore, this study aimed to compare the efficacy and safety of TMC and n-HA/PA66 in ACCF through a meta-analysis and to obtain results with a large sample size and high evidence strength to guide clinical practice.

Materials and Methods

Our study strictly adhered to the guidelines outlined in the Cochrane Handbook and Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA)[13]. This study focused on a secondary analysis of published original studies investigating the efficacy and safety of n-HA/PA66 and TMC in CSM treatment. Ethical approval was not required because our study did not involve humans or animals.

Literature Search

Two researchers conducted a comprehensive literature search using the following search terms primarily: "cervical spondylosis", "ACCF", "nano-hydroxyapatite/polyamide 66 cage", "anterior cervical fusion", and "titanium mesh cage" in Embase, PubMed, and Web of Science, Cochrane, and a locally built database from its inception to January 2023. A comprehensive search strategy was used to gather relevant literature. To ensure a thorough search, we combined subject headings and free-text terms. Additionally, we manually searched to minimize the risk of overlooking potentially valuable studies. This involved a meticulous review of the included studies and pertinent references. During the literature screening phase, two evaluators diligently examined the titles, abstracts, and full texts of the identified literature to determine if they met the predetermined inclusion criteria. This rigorous screening process aimed to ensure that study selection aligns with the research objectives and to maintain the integrity of the study's findings. Finally, consistency was ensured by cross-checking. If the two evaluators did not agree, a third evaluator was included for discussion and decision-making. The same approach was used in the data extraction phase.

Inclusion Criteria
(1) Studies involving patients diagnosed with CSM who were unresponsive to conservative treatment and required surgical intervention.
(2) Studies directly comparing the use of TMC and n-HA/PA66 in ACCF.
(3) Randomized controlled trials (RCTs) were preferred. However, non-randomized clinical controlled studies were included if RCTs were not relevant or limited. In the literature selection process, literature in various languages could be included.
(4) Publicly available studies with complete data.

Exclusion Criteria
(1) Review articles, single case reports, or studies with incomplete or insufficient data.
(2) Biomechanical and animal studies.
(3) Duplicate publications.

Data Extraction
(1) Year of publication, sample size, and length of follow-up
(2) Patient demographics: age, sex.
(3) Surgical details: operative time, intraoperative blood loss.

(4) Outcome measures: Japanese Orthopedic Association (JOA) score, visual analog scale (VAS) score, C2–7 Cobb angle, fusion rate, and settling rate.

Two researchers independently extracted the included literature, and the extracted data will be filled into a pre-designed standard data extraction summary form for pooled analysis. To verify data accuracy and consistency, conflicts emerging throughout the data extraction process will be settled by negotiation with a third researcher. Such a data extraction process can improve our study's reliability and reproducibility.

Statistical Analysis

RevMan 5.2 software (Review Manager Web, The Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analysis. Mean difference (MD) and standardized mean difference (SMD) were used as the effect measure for continuous data with the same and multiple measurement units, respectively. Moreover, relative risks (RRs) were used as an effect metric for dichotomous data. Furthermore, 95% confidence intervals (95% CI) were estimated, and statistical significance was defined as $p < 0.05$.

Heterogeneity was quantified using the I^2 statistic, with I^2 of > 75%, 50-75%, and < 50% indicating high, moderate, and low heterogeneity, respectively[14]. A random-effects model was used for statistical analysis, and subgroup or meta-regression analyses were used to explore plausible causes of heterogeneity among studies. A fixed-effects model for data synthesis and analysis was used for studies with low heterogeneity. A sensitivity analysis using an exclusion-by-exclusion approach was used to validate the robustness of the combined statistical effect sizes. A higher degree of feasibility was considered for the combined outcome measure if the effect size of a particular outcome measure did not exhibit significant changes during the sensitivity analysis process, suggesting that the translated conclusions are relatively reliable. Additionally, publication bias was assessed using funnel plots.

Quality Assessment of Included Studies

The Newcastle-Ottawa Quality Assessment Scale (NOQAS) was used to evaluate the methodological quality of the included observational studies[15,16]. The evaluation scale covers eight entries on key elements, such as study subject selection, comparison between study groups, and outcome assessment. The total score is 9, and each entry is marked with an asterisk. A study was considered high quality if it was included with an asterisk ≥ 6; otherwise, it was considered low quality[17]. Two authors assessed independent risk bias to ensure the evaluation's objectivity and accuracy. To ensure that the final evaluation results were accurate and reliable, a third author with > 3 years of experience in evaluating the quality of the literature resolved the disagreements between the two authors. Through this consultative and collaborative approach, a comprehensive and consistent assessment of risk bias is ensured, and the credibility and scientific validity of the study are improved.

Results

Search Results

Based on a predefined search strategy, electronic databases were searched, and initially screened 385 publications that might meet the inclusion criteria. Subsequently, 204 duplicate publications from multiple databases were removed from the literature management software. We conducted a comprehensive literature review to identify relevant studies for analysis. Initially, 163 studies were excluded because they did not meet the predefined inclusion criteria. The remaining 18 publications underwent a thorough full-text examination. After this meticulous review, seven studies[18-24] were deemed eligible for inclusion in the analysis because they met the strict selection criteria. Figure 1 shows the literature screening process, including the exclusion and inclusion steps. The selected studies were published from 2009 to 2020. Of these seven studies[18-24], 320 patients were included in the analysis, consisting of 172 and 148 patients assigned to the n-HA/PA66 and TMC groups, respectively.

Basic Characteristics and Quality Assessment of Included Studies

This study aimed to analyze the literature published between 2009 and 2020, focusing on the use of n-HA/PA66 for ACCF compared with TMC as a control group. Table I shows the basic characteristics of the included literature. Quality assessment scores based on the NOS scoring criteria indicated that all seven retrospective studies were of high quality, with scores ranging from 6 to 8. Table II shows the detailed evaluation of study quality.

Meta-Analysis Results

Surgical time and intraoperative blood loss

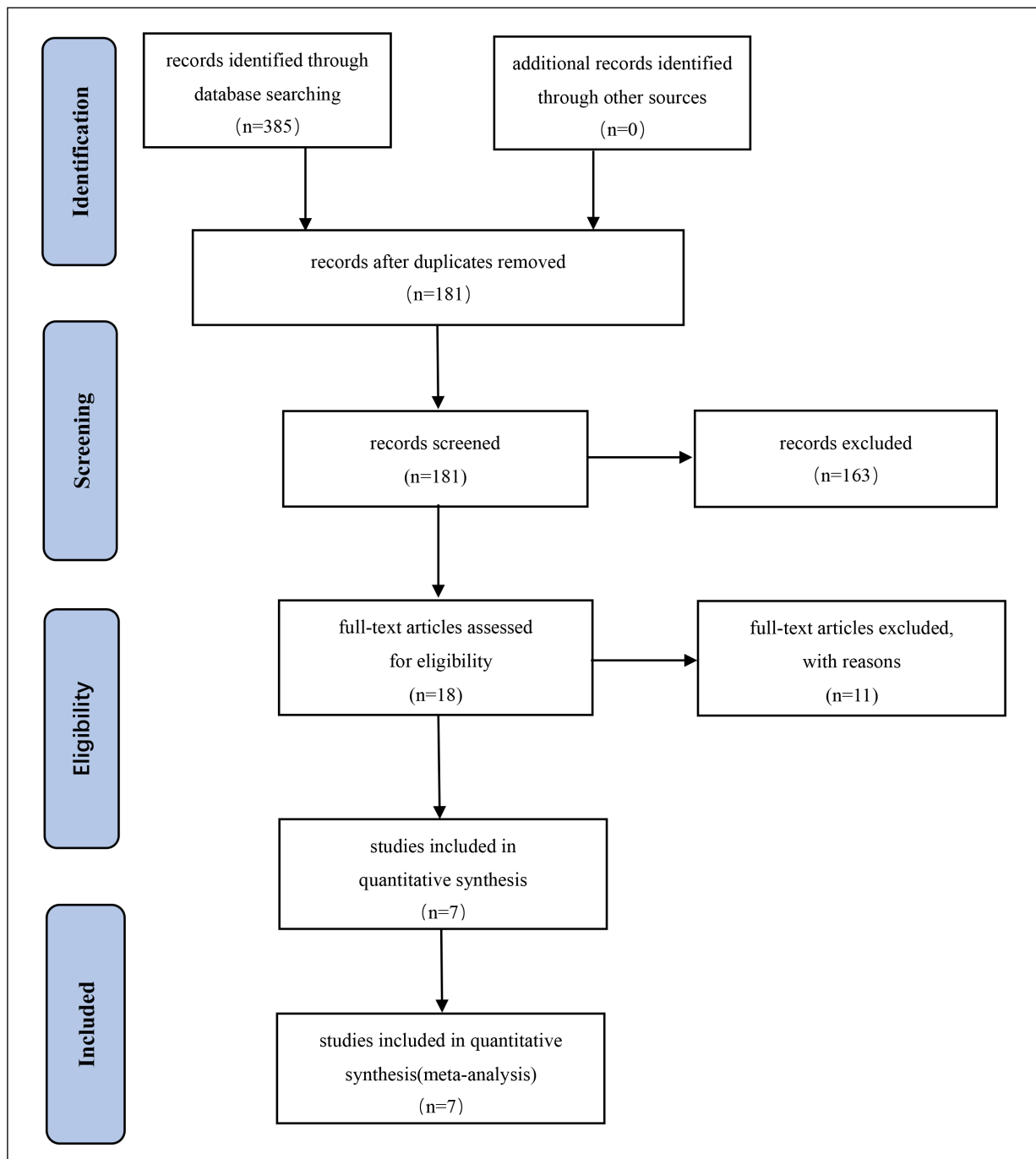Four studies[18,20,22,23] reporting surgical time showed significant heterogeneity in the meta-analysis

Figure 1. Flow diagram of study selection.

($p = 0.01$, $I^2 = 72\%$). However, after using a random effects model, the operative time was not statistically significant between the two groups [MD = -7.93, 95% CI (-16.56, 0.70), $p = 0.07$, Figure 2]. By contrast, the three included studies exhibited significant heterogeneity when considering intraoperative blood loss ($p = 0.02$, $I^2 = 76\%$). Utilizing a random-effects model for meta-analysis,

intraoperative bleeding in both groups did not show a statistically significant difference [MD = -15.77, 95% CI (-38.59, 7.05), $p = 0.18$, Figure 3].

Perioperative JOA score

The analysis of six studies[18-20,22-24] reporting preoperative JOA scores showed no significant heterogeneity ($p = 0.74$, $I^2 = 0\%$). Utilizing a fixed-ef-

Table I. The general characteristics of the included literature.

Inclusion in the study	Number of cases (male/female, cases)		Age (years)		Follow-up period (months)		Published
	TMC Group	n-HA/ PA66 Group	TMC Group	n-HA/ PA66 Group	TMC Group	n-HA/ PA66 Group	
Hu et al[18]	28/24	26/29	54.9 ± 9.5	56.5 ± 10.4	102.4 ± 4.6	103.6 ± 6.3	2019
Xi et al[19]	20/12	22/13	46.8 ± 7.2	47.6 ± 7.1	48		2013
Yuan et al[20]	11/14	29/23	55.04 ± 11.09	56.56 ± 12.13	49.80 ± 13.06	44.06 ± 13.60	2014
Liang and Zhang[24]	16/9	8/4	51.4 ± 7.5	49.7 ± 8.6	15.4 ± 4.2		2011
Zhang[23]	10/7	36/17	43.2	44.5	12		2009
Song et al[22]	23/20	21/20	50.2 ± 11.6	49.9 ± 12.4	12		2018
Ma et al[21]	16/12	14/10	56.31 ± 11.24	58.32 ± 10.52	18.43±6.32	16.77	2020

Table II. The quality assessment of the included clinical controlled trials.

Study	Section	Comparability	Exposure	NOS score
Hu et al[18]	3	2	2	7
Xi et al[19]	3	2	1	6
Yuan et al[20]	3	2	3	8
Liang and Zhang[24]	3	2	3	8
Zhang[23]	3	2	2	7
Song et al[22]	3	2	2	7
Ma et al[21]	3	2	2	7
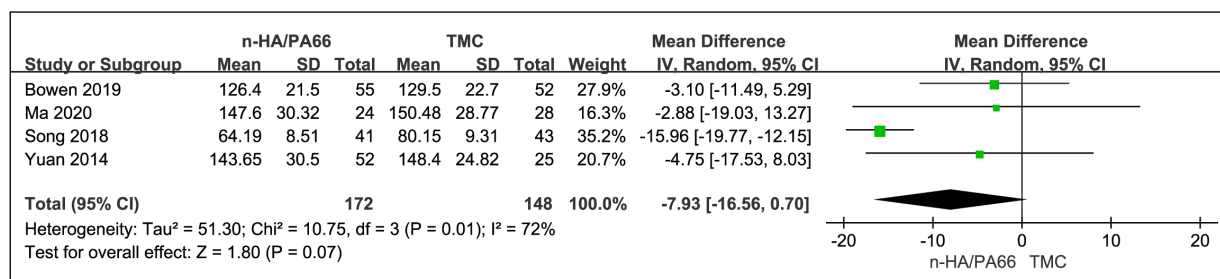
Figure 2. Forest plot of the meta-analytic estimate for surgical time.
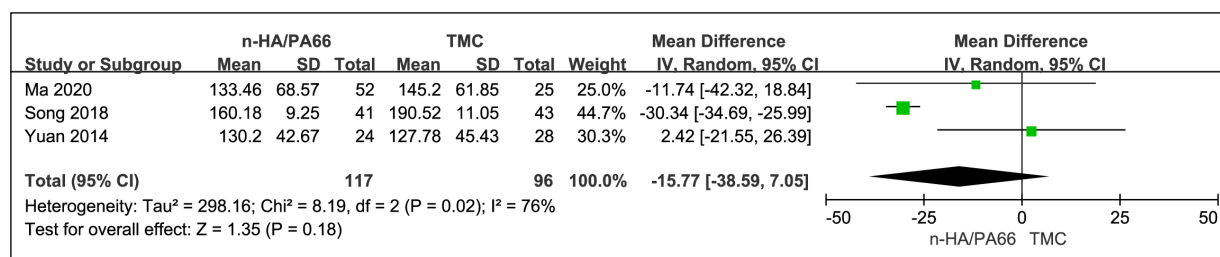
Figure 3. Forest plot of the meta-analytic estimate for intraoperative blood loss.

fects model, the preoperative JOA scores between the two groups were not statistically significantly different [MD = -0.04, 95% CI (-0.30, 0.21), p = 0.74], indicating comparable baseline conditions.

Furthermore, five publications[18-22] provided data on JOA scores at the final follow-up. No heterogeneity was observed among the studies ($p < 0.00001$, I^2 = 0%). Applying a fixed-effects model, the meta-a-

nalysis indicated that the JOA scores at the final follow-up were statistically significantly different between the two groups. Remarkably, the JOA scores at the final follow-up in the n-HA/PA66 group were higher than those in the TMC group [MD = 0.77, 95% CI (0.58, 0.97), $p < 0.00001$, Figure 4], indicating improved outcomes in terms of JOA scores, highlighting its potential as an effective intervention for the studied condition.

Perioperative VAS score

The meta-analysis of the five studies[18-22] to assess the preoperative VAS scores showed no significant heterogeneity ($p = 0.66$, $I^2 = 0\%$). After using a fixed-effects model to analyze data, no statistically significant difference in preoperative VAS scores was observed between the two groups [MD = 0.06, 95% CI (-0.21, 0.33), $p = 0.66$)]. Furthermore, the meta-analysis using a fixed-effects model of four publications with VAS scores at the final follow-up[18,20-22] ($p = 0.002$, $I^2 = 33\%$) indicated a statistically significant difference between the two groups [MD = -0.44, 95% CI (-0.71, -0.16), $p = 0.002$)]. Notably, the VAS scores at the final follow-up in the n-HA/PA66 group were lower than those in the TMC group (Figure 5).

C2–7 Cobb Angle during the perioperative period

No significant heterogeneity was found in the preoperative C2–7 Cobb angle in six studies[18-23] (p = 0.48, $I^2 = 29\%$). Using a fixed-effects model, the meta-analysis revealed that the preoperative C2–7 Cobb angle was not statistically significantly different between the two groups [MD = 0.11, 95% CI (-0.20, 0.43), $p = 0.48$, Figure 6]. Significant heterogeneity was observed in six studies[18-23] with final follow-up C2–7 Cobb angle ($p = 0.09$, $I^2 = 83\%$). A random-effects model was used to account for this heterogeneity. The meta-analysis results indicated that the difference in the C2–7 Cobb angle at the final follow-up between the two groups was not statistically significant [MD = 0.91, 95% CI (-0.16, 1.98), $p = 0.09$, Figure 7]. Therefore, the preoperative and the end-follow-up C2–7 Cobb angles were not significantly different between the two groups.

Fusion Rate at the final follow-up

A meta-analysis using a fixed-effects model showed no significant heterogeneity among five studies[19-21,23,24] ($p = 0.41$, $I^2 = 0\%$) [RR = 1.02, 95% CI (0.97, 1.07), $p = 0.41$, Figure 8]. These findings suggest that the fusion rates at the final follow-up were not statistically significantly different between the two groups.

Settling rate at the final follow-up

The settling rate at the final follow-up showed a statistically significant difference between the TMC and n-HA/PA66 groups. Meta-analysis showed no significant heterogeneity among six
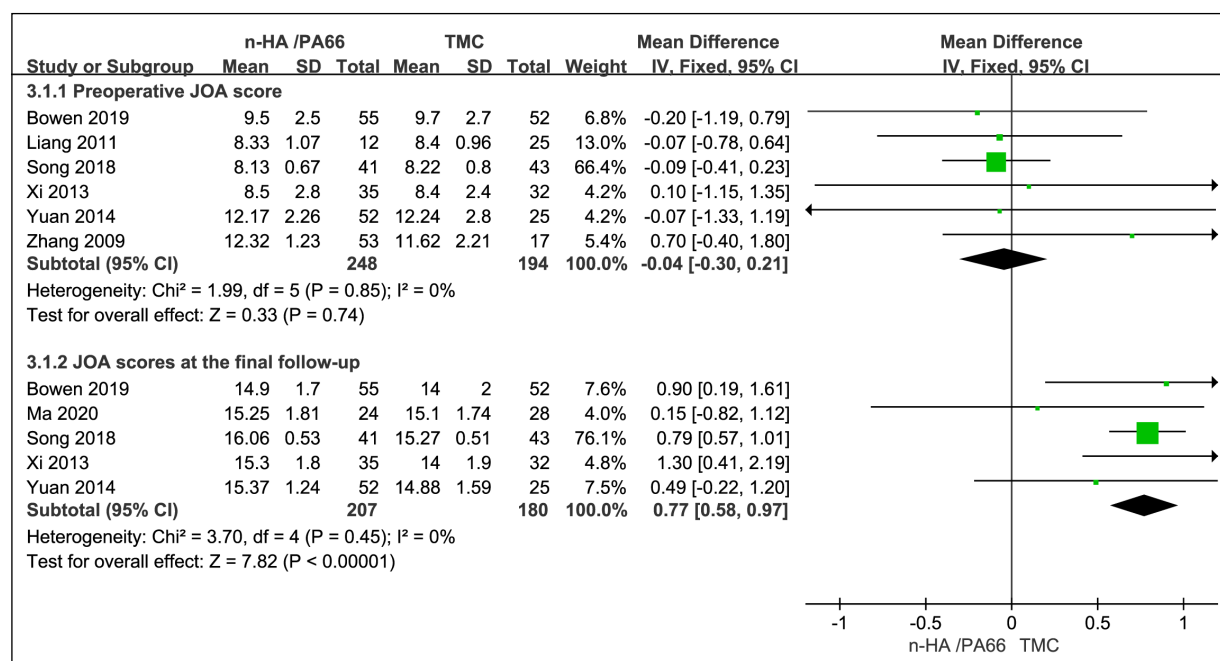

Figure 4. Forest plot of the meta-analytic estimate for perioperative JOA score and JOA scores at the final follow-up.
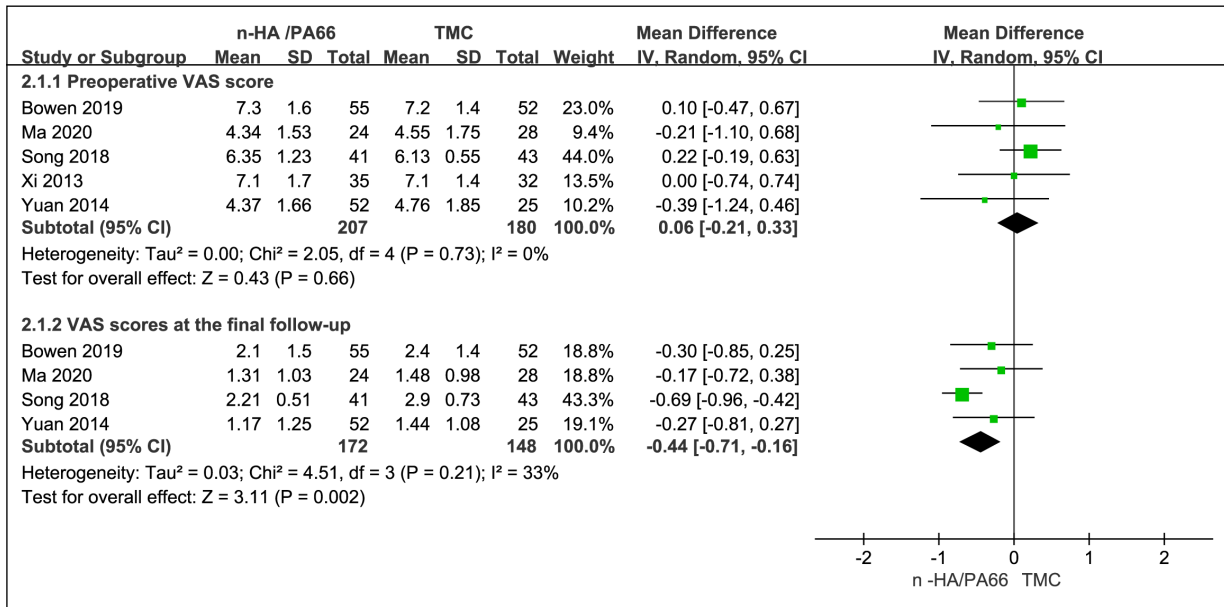
Figure 5. Forest plots of the meta-analytic estimate for perioperative VAS score and VAS scores at the final follow-up.
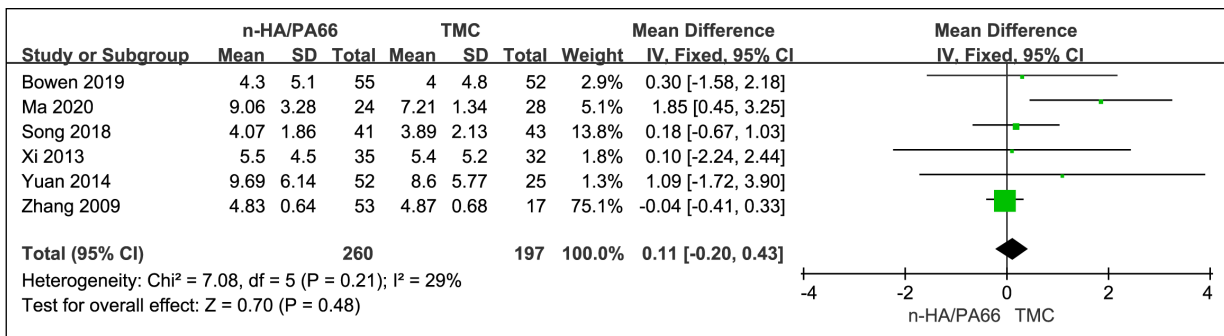

Figure 6. Forest plots of the meta-analytic estimate for C2–7 Cobb Angle during the Perioperative Period.
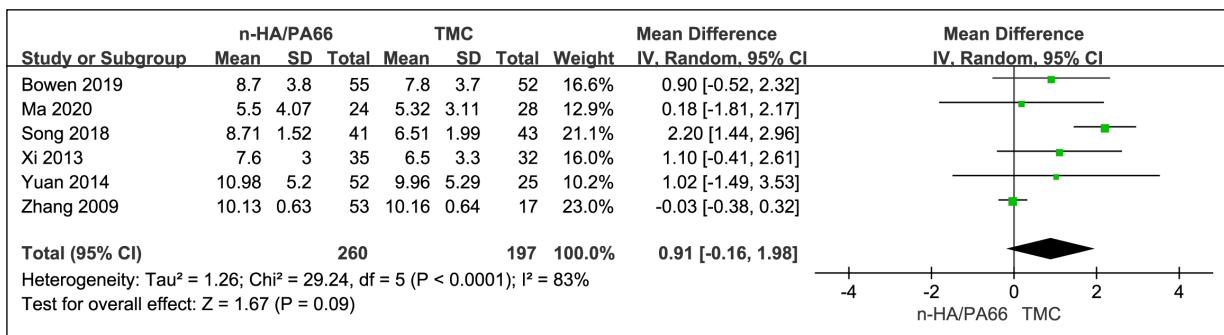
Figure 7. Forest plots of the meta-analytic estimate for C2–7 Cobb angle at the final follow-up.

studies[18-21,23,24] ($p < 0.00001$, $I^2 = 2\%$). Using a fixed-effects model, the meta-analysis showed that the final follow-up sedimentation rate in the TMC group was significantly higher than that in the n-HA/PA66 group [RR = 0.30, 95% CI (0.18, 0.48), $p < 0.00001$, Figure 9]. The statistical significance was remarkably high ($p < 0.00001$), indicating a strong association between the groups.

Figure 8. Forest plots of the meta-analytic estimate for fusion rate at the final follow-up.

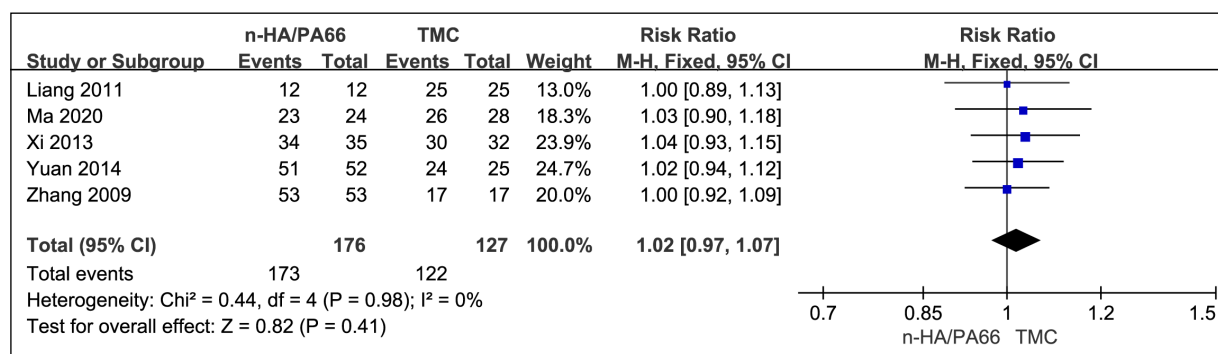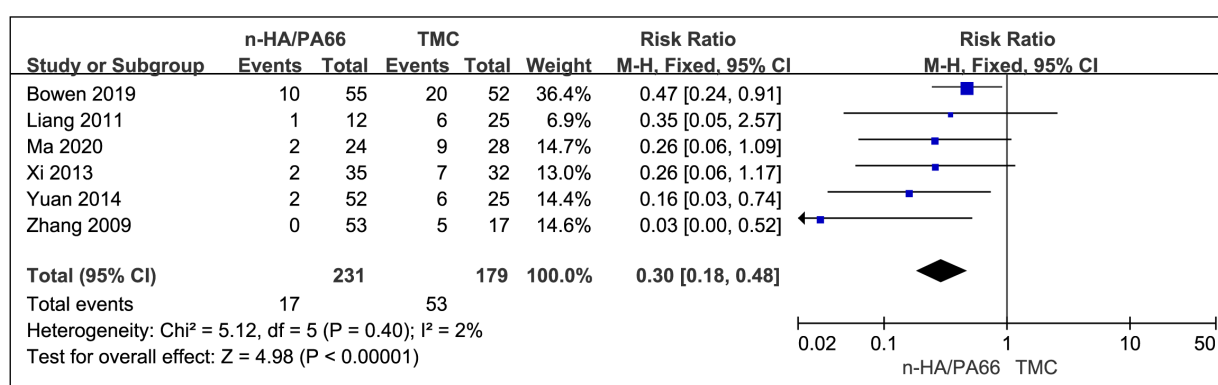**Figure 9.** Forest plots of the meta-analytic estimate for settling rate at the final follow-up.

Sensitivity and Publication Bias

One-by-one exclusion method was used for sensitivity analysis of individual outcome indicators, and the results showed no directional changes in the preoperative JOA and VAS scores and final follow-up JOA score, VAS, score, fusion rate, and sedimentation rate. This indicates good robustness and high strength of evidence for the combined outcome measures. However, after excluding the study by Yuan et al[20], the intraoperative blood loss [MD = -27.45, 95% CI (-40.66, -14.25), $p < 0.0001$] became statistically significantly different. Similarly, after excluding the study by Hu et al[18], the operative time [MD = -3.48, 95% CI (-10.14, -0.79), $p = 0.03$] and final follow-up C2–7 Cobb angle [MD = 1.37, 95% CI (0.59, 2.16), $p = 0.0006$] showed a statistically significant difference, indicating that the statistical results for these three outcome measures were highly influenced by a single study, suggesting insufficient reliability and lower strength of evidence for the combined results. When we used < 10 studies, the results for detecting publication bias were unreliable[25]. Therefore, monitoring of potential publication bias is exempted in this study.

Discussion

n-HA/PA66 is a non-metallic fusion device composed of nanoscale hydroxyapatite crystals uniformly distributed as nanoparticles within a polyamide matrix. The nanoscale hydroxyapatite crystals in n-HA/PA66 are essential inorganic components found in human bones and teeth, whereas the polyamide component possesses a structure similar to that of collagen, resulting in excellent biocompatibility. Furthermore, when implanted in the body, n-HA/PA66 forms a layer of plate- and needle-like hydroxyapatite crystals on its surface, which bridges the interface between the implant and recipient bone, ensuring tight osseointegration and maintaining excellent bioactivity[26]. It is considered a novel cervical reconstruction material[27], exhibiting favorable osteoconductive and mechanical properties, which can maintain cervical height, curvature, and mechanical stability, as well as promote fusion between adjacent vertebral bodies[28,29]. Therefore, this material is gradually becoming widely used in spinal surgery, particularly in cervical spine surgery[30-32].

Fusion rate and functional improvement are important indicators for evaluating clinical efficacy. Some studies[33,34] reported a high fusion rate after using n-HA/PA66 in anterior cervical spine surgery. Huang and Quan[33] reported a 100% implant fusion rate at 6 months postoperatively in 46 patients who underwent cervical spine surgery using n-HA/PA66 and who were followed up for 12 to 36 months, which was consistent with the retrospective study by Liang et al[32]. However, the conclusions of these studies[34,35] have not been widely accepted because of the limitations of sample size and retrospective study design. Our study supports this viewpoint because our meta-analysis showed a fusion rate of 98.3% when using n-HA/PA66 in ACCF, indicating a satisfactory fusion rate. This may be attributed to the circular design and fenestrations of n-HA/PA66, which increase the cross-sectional area, enhancing stability and promoting contact between the graft and vertebral bodies, facilitating fusion. Additionally, the improved fusion rate may be due to its elastic modulus being highly similar to that of autologous bone cortex, which can better mimic the mechanical characteristics of natural bone and better facilitate bone fusion[36,37]. The use of n-HA/PA66 in spinal surgery is both safe and effective[38-40]. Our meta-analysis demonstrated significant improvement in postoperative JOA and VAS scores for both groups compared to their respective preoperative scores. Importantly, the n-HA/PA66 group exhibited higher JOA and lower VAS scores compared to the TMC group. The clinical efficacy of n-HA/PA66 in spinal surgery should be recognized and acknowledged, as reported by Ying et al[39]. This may be related to the restoration of cervical physiological curvature because some studies[41-44] showed that the C2–7 Cobb angle and its change were positively correlated with postoperative outcomes. Nevertheless, this study, which summarized the results of multiple original studies, showed that the C2–7 Cobb angle at the final follow-up in both groups improved compared to the preoperative period, but this result did not significantly differ between the two groups. This indicates that the recovery of the C2–7 Cobb angle in the postoperative cervical spine is equivalent when using n-HA/PA66 or TMC as implant materials. Thus, both n-HA/PA66 and TMC are effective in restoring cervical physiological curvature, which may be related to the subsidence of the fusion device. Severe subsidence can lead to loss of fusion segment height, which is associated with postoperative kyphotic deformity or neurological function deterioration, thereby affecting surgical outcomes[45].

TMC has been widely used clinically as a cervical reconstruction material, and several studies[46,47] have shown satisfactory clinical outcomes. However, a common complication of TMC is the postoperative sinking of fusion, leading to a significant loss of intervertebral height[46]. Chen et al[47] reported that 19% of patients experienced TMC subsidence in their follow-up study. Similarly, Daubs et al[48] reported a 30% incidence of TMC subsidence. By contrast, Zhao et al[49] reported a 2.9% subsidence rate of n-HA/PA66 in cervical spine reconstruction, which was consistent with Yang et al[50] at 6%. Our meta-analysis yielded similar results, wherein the subsidence rate at the final follow-up for the n-HA/PA66 and TMC groups was 7.3% and 29.6%, respectively. Compared to TMC, n-HA/PA66 can effectively reduce the occurrence of postoperative fusion device subsidence. Various factors contribute to fusion device subsidence, including intraoperative endplate preservation, osteoporosis, and the properties and shape of the fusion device materials[51]. Some studies[43,44] showed that the high settling rate of the fuser was mostly caused by the short contact area of TMC with the adjacent endplates. Expansion of the contact area of TMC with the adjacent endplates can significantly decrease the settling rate. The design of n-HA/PA66 with wide annular edges increases the contact area with the adjacent endplates, thereby effectively reducing the risk of sinkage. Additionally, the fuser's low sinkage rate may be due to the n-HA/PA66's elastic modulus comparable to that of natural bone[36,37].

Limitations

However, this study has several limitations. First, all included studies were retrospective in nature, lacking high-quality RCTs. Second, the language restriction, including publications in Chinese and English, may introduce language bias. Third, the lack of detailed intraoperative documentation prevented a comprehensive comparison of the advantages and disadvantages of the two materials. Therefore, high-quality, multicenter RCTs with a larger sample size should be conducted in the future to validate the findings of the present study and obtain more reliable guidance for clinical practice[52].

Conclusions

The use of n-HA/PA66 and TMC in ACCF for CSM treatment is safe and effective, with

noteworthy clinical outcomes. However, compared with TMC, n-HA/PA66 can significantly reduce the incidence of fusion device subsidence and ensure treatment efficacy.

Conflict of Interest

Ethics Approval

Availability of Data and Materials

Acknowledgments

Informed Consent

Funding

Authors' Contributions

Jianchang Li and Bin Liang conceived and designed the study. Jianchang Li, Ye Cu performed the experiments. Jianchang Li, Ye Cu, and Bode Yi interpreted the data. Jianchang Li, Fuyu Chen, Nenggan Huang, and Bode Yi contributed reagents, materials, analysis tools. Jianchang Li wrote the first draft of the manuscript.

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