Application of nano-hydroxyapatite matrix graft in inter-vertebral fusion therapy: a meta-analysis

Kui Zhang[1†], Yandong Zhu[2†] and Wenji Wang[3*]

Abstract

Objective Nano-hydroxyapatite and its composites(nHA) have been widely used as grafts in inter-vertebral fusion. However, the safety and efficacy of the graft in inter-vertebral fusion is controversial. This meta-analysis aimed at evaluating the safety and efficacy of nHA and non-hydroxyapatite grafts (noHA) (autologous bone, etc.) in inter-body fusion.

Materials and methods A comprehensive search was performed in electronic database as follows: PubMed, EMBASE, the Cochrane Library, Web of Science, and China National Knowledge Internet (CNKI) from inception until October 2022. Clinical studies on the effect of nHA and noHA in spinal fusion were collected. Analysis of outcome indicators using RevMan 5.4 statistical software.

Results The meta-analysis showed that the operation time of patients who underwent inter-body fusion with nHA grafts was less than that of patients who underwent noHA ($p < 0.05$). Compared with the noHA group, the nHA group can achieve similar clinical effects in the fusion rate(OR=1.29,95%CI: 0.88 to 1.88,$p = 0.19$),Subsidence rate(OR=1.2,95%CI:0.44 to 3.28,$p = 0.72$), inter-vertebral space height(SMD=0.04,95%CI:-0.08 to 0.15,$p = 0.54$),Cobb angle(SMD=0.21,95%CI: 0.18 to 0.6,$p = 0.21$),Blood loss(SMD=-36.58,95%CI: -81.45 to 8.29,$p = 0.11$),operative time in 12 months(SMD=-5.82,95%CI: -9.98 to -1.67,$p = 0.006$) and in the final follow-up(SMD=-0.38,95%CI: -0.51 to -0.26,$p < 0.00001$),ODI(SMD=0.68,95%CI: -0.84 to 2.19,$p = 0.38$), VAS(SMD=0.17,95%CI: -0.13 to 0.48,$p = 0.27$) and adverse events(OR=0.98,95%CI: 0.66 to 1.45,$p = 0.92$), and the differences are not statistically significant.

Conclusion This meta-analysis suggests that nHA matrix grafts are similar to noHA grafts in the safety and efficacy of spinal reconstruction, and are an ideal material for inter-vertebral bone grafting.

Keywords Nano-hydroxyapatite, Inter-vertebral fusion, Meta-analysis, Bone graft

†Kui Zhang and Yandong Zhu contributed equally to this work.

*Correspondence:
Wenji Wang
ldyyjzwwj@163.com
¹ The First Clinical Medical College of Lanzhou University, Lanzhou 730000, China
² Department of Orthopedics, Ninth Hospital of Xi'An, Xi'An 710000, China
³ Department of Orthopedic, The First Clinical Medical College of Lanzhou University, Lanzhou 730000, China

Introduction

Inter-body fusion is a routine operation for the treatment of spinal degenerative diseases [1]. It achieves clinical effects such as correcting deformity, reconstructing spinal stability, and relieving pain by accelerating bone fusion [2]. Although inter-vertebral fusion is widely used in clinical practice and mature in technology, different grafts used in the operation have different effects on the functional improvement, cone sedimentation rate and cone fusion rate of patients undergoing fusion surgery [3–9].

Zhang *et al. BMC Musculoskeletal Disorders*   (2023) 24:427

Page 2 of 11

Nano-hydroxyapatite (nHA) is the main mineral in natural bones. Because of its similar chemical and physical properties to human bones, good biological activity and bone conductivity, it has a broad environment in medical applications [10, 11]. nHA matrix graft is a new type of bone reconstruction and bone repair material in recent years. It has been widely used in clinical practice and has achieved good clinical results [12]. Relevant literature studies have shown that nHA grafts have stable biomechanics, similar elastic modulus to the bone tissue, and good biocompatibility [13]. In patients with inter-vertebral fusion, it has the characteristics of less complication, high fusion rate and good bone resorption. It is a widely used bone graft filling material [14, 15]. At present, there have been some clinical studies on the safety and efficacy of nHA grafts and noHA matrix grafts in inter-vertebral fusion [14, 16–26]. Some research conclusions [14, 19, 23, 26, 27] is controversial, but no relevant systematic analysis has been found to demonstrate these conclusions. Therefore, this study collected relevant clinical studies, to take a meta-analysis method to analyze the safety and efficacy of nHA matrix graft in inter-body fusion.

Material and methods

Data sources and searches

This study was performed using a prior established protocol, and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension Statement for systematic reviews incorporating network meta-analyses.

An extensive search of PubMed, Web of Science, China National Knowledge Internet (CNKI), EMBASE, and the Cochrane Library from the establishment date of the database to October 2022 was used the following key search terms: "hydroxyapatite", "bone graft", "Bone Transplantation", "spine", "lumbar vertebrae", "thoracic vertebra", "cervical vertebra", "Arthrodesis". Lists of references cited in relevant systematic reviews and included trials were also screened. Two investigators conducted the search independently.

Inclusion and exclusion criteria

Inclusion criteria were as follows:(i) Retrospective case–control studies (RPCT), randomised controlled trials (RCT), prospective case–control studies (PCCT); (ii) Patients must undergo inter-vertebral fusion surgery; (iii) Patients were followed up for more than 24 weeks; (iv) sufficient published data to estimate odds ratio (OR), or standardized mean difference (SMD) with a 95% confidence interval (CI).

Studies were considered exclusion for this study if they met the following criteria:(i) meeting proceedings, abstracts, letters, editorials, reviews or case reports; (ii) Research without a full-text (iii) Studies lacking comparable results; (iv) no outcomes of interests; and (v) repeated reports.

Study selection

Two researchers independently developed the search strategy and sifted through all the initial literature results. Initial literature screening was performed by evaluating the titles and abstracts of the studies. The final two researchers determined the final inclusion literature by reading the full text according to establish inclusion and exclusion criteria. Disagreements on inclusion were resolved through discussion and consensus.

Outcome measures

Two researchers independently extracted available data from the included literature for analysis by reading the full text. The basic characteristics of the study (author, publication date, design type, publication country), demographic data of patients (age, sample size, follow-up time, surgical method) and the main outcome indicators of the study (fusion rate, subsidence rate, inter-vertebral space height (IH), Cobb angle, blood loss, operative time, the Oswestry Disability.

Index (ODI), the Visual Analogue Scale score (VAS), adverse events) were extracted from the final included study.

Data quality assessment

The two researchers independently assessed the quality of the included studies based on the Newcastle–Ottawa Scale (NOS), which covered three areas: object selection, condition suitability and exposure. The highest score of each study was nine, and ≥ 6 were considered to be superior-quality studies. Disagreements regarding inclusion were resolved through discussion and consensus.

Data synthesis and analysis

Statistical analyses were performed using Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020. The results for the dichotomous effect size are computed using the OR and the continuous effect size results from SMD.A 95% CI were determined for each effect size. Chi-squared tests and I-squared (I^2) statistics were tested for the heterogeneity in each study. The heterogeneity of each study was tested by Chi-squared tests and I-squared (I^2) statistics. When $p > 0.1$ and $I^2 < 50\%$, with low heterogeneity, the analysis was performed using a fixed effect model. Instead, a random effect model was applied to the analysis. Sensitivity analysis was performed by excluding some studies and calculating the effect results.

Zhang *et al. BMC Musculoskeletal Disorders*   (2023) 24:427

Page 3 of 11

Results

A total of 484 relevant studies were retrieved from the relevant databases. After removing duplicates, 298 articles remained. Then, 158 studies were discarded by title and summary reading. Through full-text reading of the remaining 140 papers, 121 studies were excluded due to incomplete full-text, inconsistencies, or missing results on the effect of the study. A total of 19 studies [4, 14, 16, 18–33] were included in the meta-analysis (Fig. 1). In addition, all included studies can be considered to be of relatively high quality based on the results of the

NOS rating scale. See Table 1 for more detailed basic features.

Fusion rate

The follow-up time for the fusion rate varied widely, ranging from 6 to 84 months. Therefore, the subgroup analysis is based on the time period.

Fusion rates at 12 months after surgery from seven studies [14, 19, 20, 22, 23, 28, 31] including 919 patients were available for analysis. A fixed-effect model was adopted as the heterogeneity among included studies was
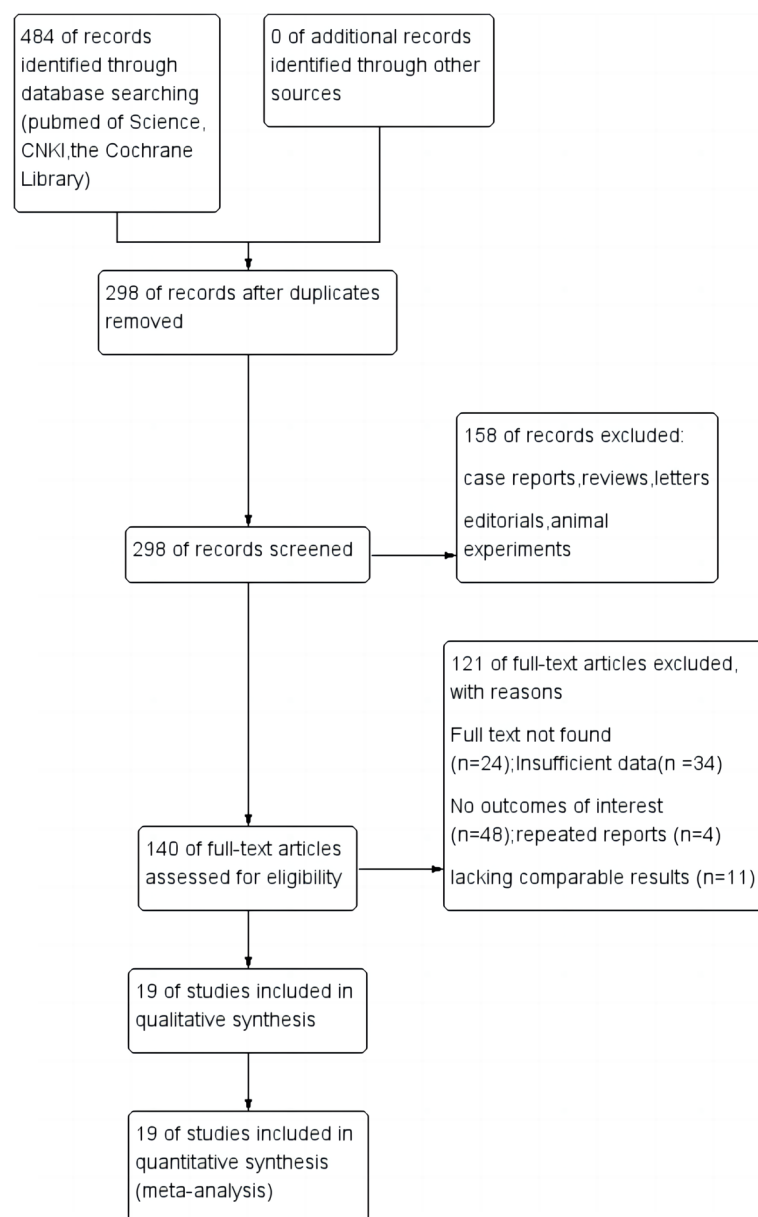

Fig. 1 PRISMA flow diagram of study selection for the current meta-analysis

Zhang *et al. BMC Musculoskeletal Disorders*   (2023) 24:427

Page 4 of 11

Table 1 Basic characteristics of enrolled studies

Author/year	Country	Study design	Age (years)	Sample Size nHA/noHA(n)	Type of surgery	Outcome indicators	Follow-up time (months)	NOS score
D.Neen 2006 [16]	UK	PCCT	49/48	50/50	PLIF	①,⑨	24	7
E.Dawson 2009 [19]	USA	PCCT	55.9/56.9	25/21	PLDIF	①,⑤,⑥,⑦,⑨	24	8
X.H.Liu 2012 [30]	China	PCCT	51.4/52.4	31/26	ACDF	①,②,③,④,⑥,⑨	24	7
J.X.Liang 2018 [29]	China	PCCT	50.5/52.5	124/50	ACDF	①,②,③,④,⑤,⑥,⑦,⑧	52	8
C.Zhu 2021 [26]	China	PCCT	54.5/55.3	32/32	TLIF	①,③,④,⑤,⑥,⑧	47	7
T.Yoshii 2021 [25]	Japan	PCCT	70.2/73.8	46/46	PLIF	①,⑨	24	8
J.Delecrin 2000 [32]	France	RCT	18.2/17.5	28/30	PLIF	④,⑤,⑥,⑨	24	8
J.R.McConnell 2003 [33]	UK	RCT	47/47	13/16	ACDF	①,②,⑨	24	8
P.Korovessis 2005 [27]	Greece	RCT	58/61	20/19	PLDIF	⑤,⑥,⑦,⑧	48	8
J.R.Dimar 2009 [14]	USA	RCT	53.2/52.3	239/224	PLDIF	①,⑤,⑥,⑨	24	7
N.H.vonderHoeh 2017 [22]	Germany	RCT	64.3/65.6	24/24	TLIF	①,⑦,⑧,⑨	12	8
J.H.Cho 2017 [21]	Korea	RCT	64.9/62	42/51	PLDIF	①,⑦,⑧,⑨	6	8
M.Rickert 2019 [23]	Germany	RCT	60.6/66.1	20/20	ALIF	①,⑧,⑨	12	8
W.Chen 2020 [28]	China	RCT	48.6/48	19/10	TLIF	①,③,④,⑤,⑥,⑦,⑨	36	7
B.L.Ma 2016 [31]	China	RCT	49.2/48	20/10	TLIF	①,④,⑤,⑥,⑦,⑨	12	7
W.C.Chang 2009 [18]	China	RPCT	58.5/51.39	22/23	ACDF	①,⑨	6	7
Q.x.Deng 2016 [20]	China	RPCT	53.2/53.6	124/142	TLIF	①,②,③,④,⑤,⑥,⑧,⑨	47	8
B. Hu 2019 [4]	China	RPCT	52.5/51.3	47/51	ACDF	①,②,③,④,⑤,⑥,⑧,⑨	84	7
Tayfun Cakir 2021 [24]	Turkey	RPCT	61.4/66.1	54/51	PLIF	③,⑦,⑧,⑨	60	8

PCCT Prospective case–control study, *RCT* Randomized controlled study, *RPCT* Retrospective case–control study, *PLIF* Posterior lumbar intertransverse fusion, *PLDIF* Posterior lumbar decompression and intertransverse fusion, *ACDF* Anterior cervical decompression and fusion, *TLIF* Transforaminal lumbar inter-body fusion. ①fusion rate,②Subsidence rate,③inter-vertebral space height,④Cobb angle,⑤blood loss,⑥operative time,⑦ODI⑧VAS,⑨adverse events

relatively low (Chi^2 = 6.29, p = 0.39, I^2 = 5%) (Fig. 2). As a result, the amount of fusion rate in nHA patients was no significant difference in noHA patients (OR = 1.29,95%CI: 0.88 to 1.88, p = 0.19).

Data on fusion rates at final follow-up after surgery were assessed in 16 studies [4, 14, 16, 18–23, 25, 26, 28–31, 33], including 1660 patients. Low heterogeneity was observed across each study (Chi^2 = 19.27, p = 0.08, I^2 = 38%), so the fixed-effect model was adopted. Again, the results exhibited no significant difference in the fusion rate between the two groups at the final follow-up (OR = 1.24,95%CI: 0.84 to 1.81, p = 0.28) (Fig. 2).

Subsidence rate

A total of five included studies [4, 20, 29, 30, 33] with 725 patients examined the settling rates in both groups. The random-effect model was then employed because of high heterogeneity (Chi^2 = 8.58, p = 0.0007, I^2 = 53%) (Fig. 3). It was not significantly different between the two groups (OR = 1.2,95%CI:0.44 to 3.28, p = 0.72).

Inter-Vertebral space height (IH)

Seven studies [4, 20, 24, 26, 28–30] consisting of 864 patients documented IH. The heterogeneity among

included studies was relatively low (Chi^2 = 3.98, p = 0.68, I^2 = 0%) and the fixed-effect model was used for analysis (Fig. 4). It was not significantly different between the two groups (SMD = 0.04,95%CI: -0.08 to 0.15, p = 0.54).

Cobb angle

Regarding the Cobb angle, 842 patients from eight studies [4, 20, 26, 28–32] were pooled in the analysis. There was low heterogeneity across each study (Chi^2 = 5.62, p = 0.58, I^2 = 0%) and we used the fixed-effect model (Fig. 5). No significant difference was found between the nHA and the noHA groups (SMD = 0.21,95%CI: 0.18 to 0.6, p = 0.21).

Blood loss

With respect to blood loss during surgery, ten studies [4, 14, 19, 20, 26–29, 31, 32] consisting of 1267 patients were pooled for this outcome using a random effect model due to high heterogeneity. (Chi^2 = 107.33, p < 0.0001, I^2 = 92%) (Fig. 6). Again, the results did not show a significant difference in blood loss between the two groups (SMD = -36.58,95%CI: -81.45 to 8.29, p = 0.11).
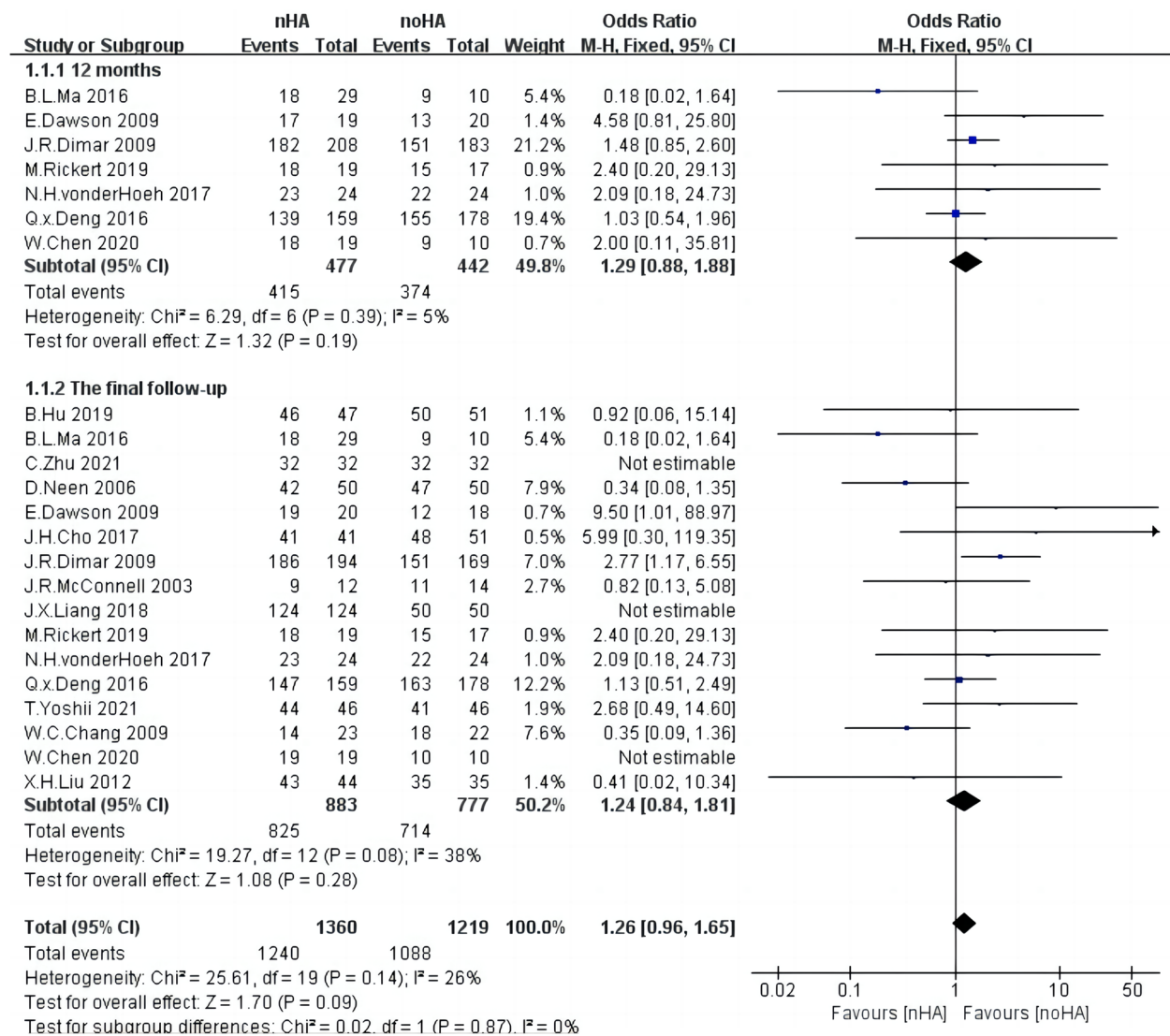
Study or Subgroup	nHA Events	Total	noHA Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 12 months						
B.L.Ma 2016	18	29	9	10	5.4%	0.18 [0.02, 1.64]
E.Dawson 2009	17	19	13	20	1.4%	4.58 [0.81, 25.80]
J.R.Dimar 2009	182	208	151	183	21.2%	1.48 [0.85, 2.60]
M.Rickert 2019	18	19	15	17	0.9%	2.40 [0.20, 29.13]
N.H.vonderHoeh 2017	23	24	22	24	1.0%	2.09 [0.18, 24.73]
Q.x.Deng 2016	139	159	155	178	19.4%	1.03 [0.54, 1.96]
W.Chen 2020	18	19	9	10	0.7%	2.00 [0.11, 35.81]
Subtotal (95% CI)		477		442	49.8%	**1.29 [0.88, 1.88]**
Total events	415		374			
Heterogeneity: Chi² = 6.29, df = 6 (P = 0.39); I² = 5%						
Test for overall effect: Z = 1.32 (P = 0.19)						
1.1.2 The final follow-up						
B.Hu 2019	46	47	50	51	1.1%	0.92 [0.06, 15.14]
B.L.Ma 2016	18	29	9	10	5.4%	0.18 [0.02, 1.64]
C.Zhu 2021	32	32	32	32		Not estimable
D.Neen 2006	42	50	47	50	7.9%	0.34 [0.08, 1.35]
E.Dawson 2009	19	20	12	18	0.7%	9.50 [1.01, 88.97]
J.H.Cho 2017	41	41	48	51	0.5%	5.99 [0.30, 119.35]
J.R.Dimar 2009	186	194	151	169	7.0%	2.77 [1.17, 6.55]
J.R.McConnell 2003	9	12	11	14	2.7%	0.82 [0.13, 5.08]
J.X.Liang 2018	124	124	50	50		Not estimable
M.Rickert 2019	18	19	15	17	0.9%	2.40 [0.20, 29.13]
N.H.vonderHoeh 2017	23	24	22	24	1.0%	2.09 [0.18, 24.73]
Q.x.Deng 2016	147	159	163	178	12.2%	1.13 [0.51, 2.49]
T.Yoshii 2021	44	46	41	46	1.9%	2.68 [0.49, 14.60]
W.C.Chang 2009	14	23	18	22	7.6%	0.35 [0.09, 1.36]
W.Chen 2020	19	19	10	10		Not estimable
X.H.Liu 2012	43	44	35	35	1.4%	0.41 [0.02, 10.34]
Subtotal (95% CI)		883		777	50.2%	**1.24 [0.84, 1.81]**
Total events	825		714			
Heterogeneity: Chi² = 19.27, df = 12 (P = 0.08); I² = 38%						
Test for overall effect: Z = 1.08 (P = 0.28)						
Total (95% CI)		1360		1219	100.0%	**1.26 [0.96, 1.65]**
Total events	1240		1088			
Heterogeneity: Chi² = 25.61, df = 19 (P = 0.14); I² = 26%						
Test for overall effect: Z = 1.70 (P = 0.09)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.87), I² = 0%						

Fig. 2 The forest plot of fusion rate of nHA group versus noHA group

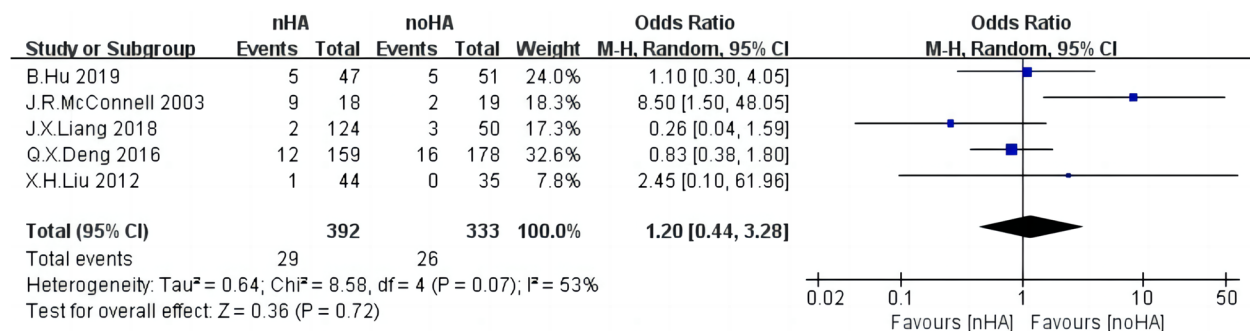| Study or Subgroup	nHA Events	Total	noHA Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
B.Hu 2019	5	47	5	51	24.0%	1.10 [0.30, 4.05]
J.R.McConnell 2003	9	18	2	19	18.3%	8.50 [1.50, 48.05]
J.X.Liang 2018	2	124	3	50	17.3%	0.26 [0.04, 1.59]
Q.X.Deng 2016	12	159	16	178	32.6%	0.83 [0.38, 1.80]
X.H.Liu 2012	1	44	0	35	7.8%	2.45 [0.10, 61.96]
Total (95% CI)		392		333	100.0%	**1.20 [0.44, 3.28]**
Total events	29		26			
Heterogeneity: Tau² = 0.64; Chi² = 8.58, df = 4 (P = 0.07); I² = 53%						
Test for overall effect: Z = 0.36 (P = 0.72)						

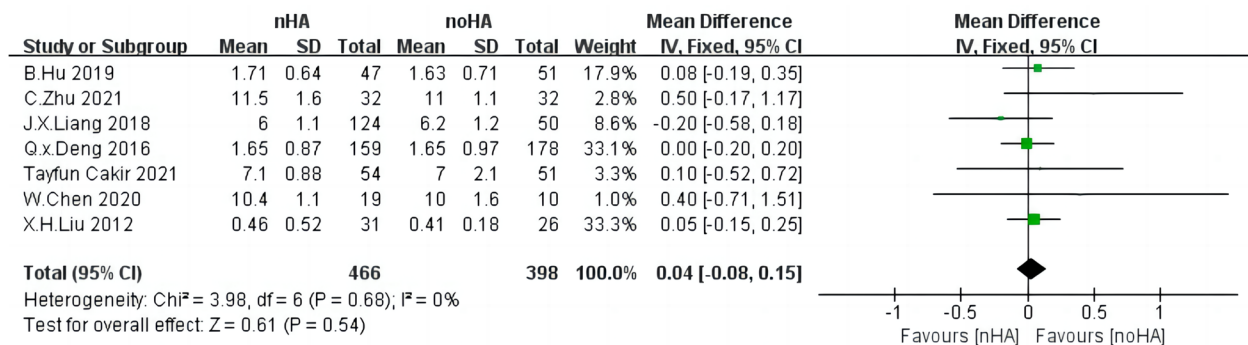**Fig. 3** The forest plot of Subsidence rate of nHA group versus noHA group

Fig. 4 The forest plot of inter-vertebral space height of nHA group versus noHA group
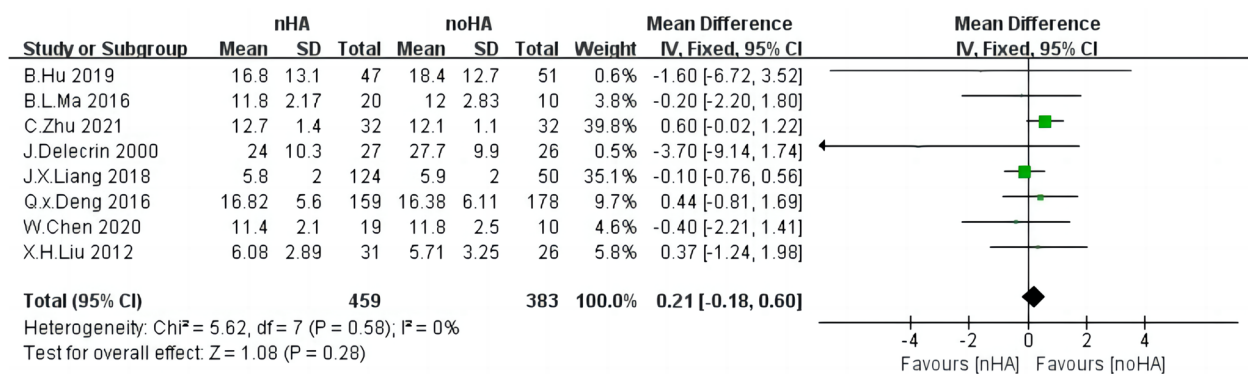

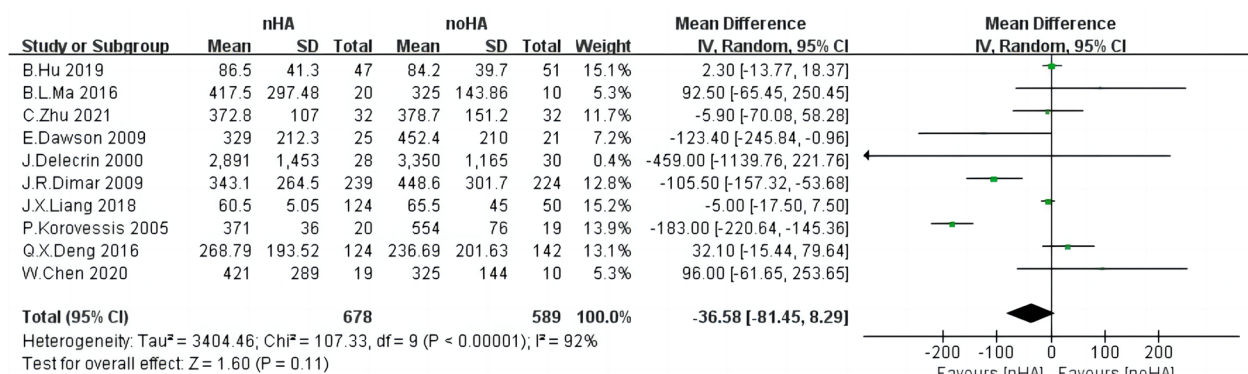**Fig. 5** The forest plot of Cobb angle of nHA group versus noHA group

Fig. 6 The forest plot of Blood loss of nHA group versus noHA group

Operative time

Regarding the operation time, since the data included in the analysis were taken in minutes and hours, the data were subgroup and analyzed in subgroups by Minutes and Hours, respectively.

A total of nine inclusion studies [4, 20, 26–32] involving 815 patients in the Minutes group and two inclusion studies [14, 19] involving 509 patients in the Hours group examined the timing of surgery. There is low heterogeneity among the studies (Chi^2 = 7.18, p = 0.52,

Study or Subgroup	nHA Mean	nHA SD	nHA Total	noHA Mean	noHA SD	noHA Total	Weight	Mean Difference IV, Fixed, 95% CI
B.Hu 2019	87.4	21.5	47	91.5	22.7	51	22.5%	-4.10 [-12.85, 4.65]
B.L.Ma 2016	175.75	26.47	20	183.5	45.65	10	1.8%	-7.75 [-38.33, 22.83]
C.Zhu 2021	193	25.7	32	201.2	24.2	32	11.5%	-8.20 [-20.43, 4.03]
J.Delecrin 2000	254	36	28	244	52	30	3.3%	10.00 [-12.89, 32.89]
J.X.Liang 2018	90.15	30.57	124	95.7	28.1	50	19.2%	-5.55 [-15.02, 3.92]
P.Korovessis 2005	118	18	20	135	18	19	13.5%	-17.00 [-28.30, -5.70]
Q.x.Deng 2016	163.31	34.25	124	164.82	40.22	142	21.5%	-1.51 [-10.46, 7.44]
W.Chen 2020	169	25	19	184	46	10	1.8%	-15.00 [-45.65, 15.65]
X.H.Liu 2012	93.7	35.2	31	97.5	37.6	26	4.8%	-3.80 [-22.84, 15.24]
Total (95% CI)			**445**			**370**	**100.0%**	**-5.82 [-9.98, -1.67]**

Heterogeneity: Chi² = 7.18, df = 8 (P = 0.52); I² = 0%
Test for overall effect: Z = 2.75 (P = 0.006)

Study or Subgroup	nHA Mean	nHA SD	nHA Total	noHA Mean	noHA SD	noHA Total	Weight	Mean Difference IV, Fixed, 95% CI
E.Dawson 2009	2.4	0.7	25	2.6	0.8	21	8.2%	-0.20 [-0.64, 0.24]
J.R.Dimar 2009	2.5	0.09	239	2.9	1	224	91.8%	-0.40 [-0.53, -0.27]
Total (95% CI)			**264**			**245**	**100.0%**	**-0.38 [-0.51, -0.26]**

Heterogeneity: Chi² = 0.73, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 5.97 (P < 0.00001)

Fig. 7 The forest plot of operative time of nHA group versus noHA group

$I^2 = 0\%$) and (Chi$^2 = 0.73$, $p = 0.39$, $I^2 = 0\%$), the fixed-effect model was used for analysis (Fig. 7). The operation time of nHA patients was significantly less than the time observed in noHA patients (SMD = -5.82, 95%CI: -9.98 to -1.67, $p = 0.006$) and (SMD = -0.38, 95%CI: -0.51 to -0.26, $p < 0.00001$).

ODI

Regarding ODI, 736 patients from seven studies [20, 21, 24, 27–29, 31] were pooled in the analysis. There was low heterogeneity across each study (Chi$^2 = 0.27$, $p = 1$, $I^2 = 0\%$) and we used the fixed-effect model (Fig. 8). The results exhibited no significant difference in the ODI between the two groups (SMD = 0.68, 95%CI: -0.84 to 2.19, $p = 0.38$).

VAS

Eight studies [4, 20–24, 26, 29] consisting of 884 patients documented VAS. The fixed-effect model was employed because of low heterogeneity (Chi$^2 = 13.28$, $p = 0.07$, $I^2 = 47\%$). No significant difference was found between nHA and noHA groups (SMD = 0.17, 95%CI: -0.13 to 0.48, $p = 0.27$) (Fig. 9).

Adverse events

For adverse events, 1,136 patients from 12 studies [4, 14, 16, 18, 19, 21–24, 28, 32, 33] were pooled in the analysis. A fixed-effect model was adopted as the heterogeneity among included studies was relatively low (Chi$^2 = 6.68$, $p = 0.82$, $I^2 = 0\%$) (Fig. 10). As a result, the amount of fusion rate in nHA patients was significantly less than that in noHA patients (OR = 0.98, 95%CI: 0.66 to 1.45, $p = 0.92$).
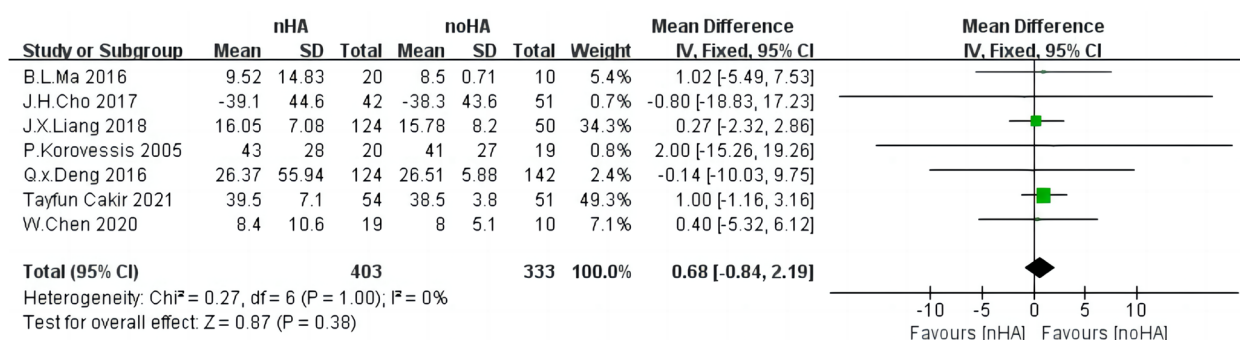
Study or Subgroup	nHA Mean	nHA SD	nHA Total	noHA Mean	noHA SD	noHA Total	Weight	Mean Difference IV, Fixed, 95% CI
B.L.Ma 2016	9.52	14.83	20	8.5	0.71	10	5.4%	1.02 [-5.49, 7.53]
J.H.Cho 2017	-39.1	44.6	42	-38.3	43.6	51	0.7%	-0.80 [-18.83, 17.23]
J.X.Liang 2018	16.05	7.08	124	15.78	8.2	50	34.3%	0.27 [-2.32, 2.86]
P.Korovessis 2005	43	28	20	41	27	19	0.8%	2.00 [-15.26, 19.26]
Q.x.Deng 2016	26.37	55.94	124	26.51	5.88	142	2.4%	-0.14 [-10.03, 9.75]
Tayfun Cakir 2021	39.5	7.1	54	38.5	3.8	51	49.3%	1.00 [-1.16, 3.16]
W.Chen 2020	8.4	10.6	19	8	5.1	10	7.1%	0.40 [-5.32, 6.12]
Total (95% CI)			**403**			**333**	**100.0%**	**0.68 [-0.84, 2.19]**

Heterogeneity: Chi² = 0.27, df = 6 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.87 (P = 0.38)

Fig. 8 The forest plot of ODI nHA group versus noHA group. ODI: the Oswestry Disability Index

Zhang *et al. BMC Musculoskeletal Disorders*   (2023) 24:427
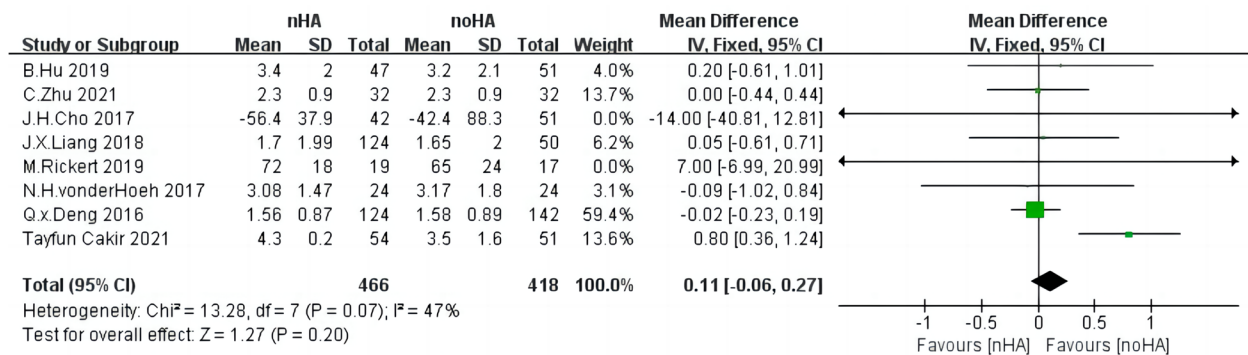
Page 8 of 11

Fig. 9 The forest plot of VAS of nHA group versus noHA group. VAS: the Visual Analogue Scale score
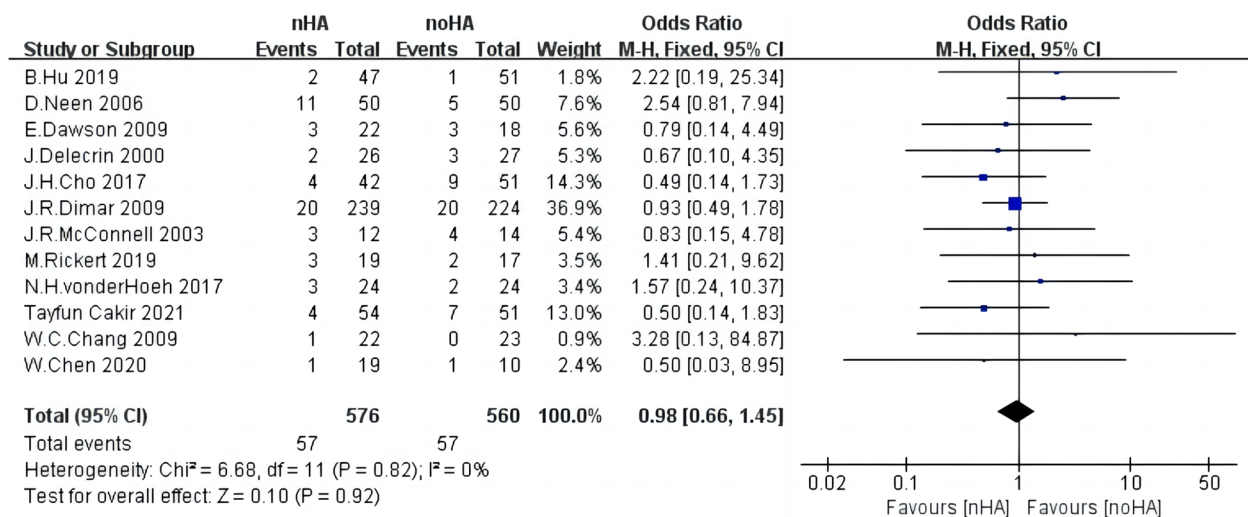

Fig. 10 The forest plot of adverse events of nHA group versus noHA group

Discussion

nHA is the main mineral in natural bone. Due to its excellent mechanical properties, biocompatibility, and similar chemical and physical properties to human bone, it has attracted considerable attention in the preparation of prosthetic implants, scaffolds, and artificial bone cement [34]. However, the individual application of nHA is limited by its poor mechanical properties, and thus its application is severely limited. With the development of bio-engineering techniques and materials science, nHA can be combined with a variety of alternative materials to obtain composites with high strength and elevated osteogenic activity, which is a critical direction for bone tissue engineering research. At present, nHA is mainly combined with the following materials [35–37]: bioactive factors, synthetic polymer materials (polyhydroxy glycolic acid, polyetheretherketone, polyethylene, polylactic acid, polyamide, etc.), natural polymer materials (cellulose, silk fibroin, dextran, collagen, chitosan, etc.), and it has also

been reported in literature that nHA can be combined with antibiotics, antitumor drugs, bone marrow mesenchymal stem cells and insulin-like growth factors to obtain the desired specific function. The nHA compound has excellent mechanical and biological properties. It has clear advantages over pure nHA materials and has great potential for applications in bone tissue engineering.

In this study, we compared intra- and post-operative clinical and imaging outcomes of nHA matrix composite bone grafts and noHA grafts in inter-body fusion. Spinal fusion was performed in studies involving either the cervical or thoracic or lumbar vertebra. Patients' ages varied widely among the included studies, but there was no significant difference between the experimental and control groups within each study. Operation time and intraoperative blood loss are critical indicators that reflect the safety of the surgery. Some studies [20, 28, 31] have shown that intraoperative blood loss is greater in nHA than in the control group,

Zhang *et al. BMC Musculoskeletal Disorders*   (2023) 24:427

Page 9 of 11

which may be due to the surgeon's master's degree in surgical skills. Excessive intraoperative bleeding may lead to haemorrhagic shock and damage to vital organs, which can be life-threatening in severe cases. Multiple experiments included in the meta-analysis showed that inter-body fusion did not significantly increase the risk of major intraoperative bleeding in the nHA group. This conclusion is controversial due to the large heterogeneity among the included studies.

In general, the longer the procedure, the higher the risk of intraoperative complications such as asphyxia and anesthesia accidents. Most of the included studies [4, 20, 26, 28–32] showed that there was no statistical difference in the operating time between the two groups, but meta-analysis found that the operation time of the experimental group was significantly less than that of the control group, indicating that the operation time of nHA matrix graft was less and it was safer for patients undergoing surgery. This study used the incidence of adverse events as a measure of postoperative safety and found that interbody fusion with nHA matrix grafts did not significantly increase the incidence of postoperative complications, consistent with Cakir's and Chen's findings [24, 28].

It has been shown that the different graft materials used in spinal fusion surgery can directly affect bone graft fusion rate, inter-vertebral space height and fusion segment curvature recovery [38, 39]. The results of this meta-analysis showed that: Two different materials of graft showed similar fusion rate and collapse rate, this could be due to these two kinds of material of graft has similar elastic modulus, and both by increasing the friction between the graft and endplate and dispersed pressure on the surface of the implant to prevent graft migration and sinking, help maintains the height of the inter-vertebral fusion segments and curvature fusion segments, to achieve the stability of the cone segments, it can be inferred that the nHA matrix graft has good biomechanical properties. There was no significant difference in VAS scores and ODI between the nHA and noHA groups. Overall, the meta-analysis of each test metric concluded that nHA and its related materials have stable therapeutic effects and clear advantages in terms of inter-body fusion, short operating time, high conical fusion rate and low incidence of adverse events, suggesting that nHA matrix composites are a safe and effective biomaterial.

In this meta-analysis, there is heterogeneity between nHA and noHA groups in the research of Subsidence rate. The study of J.R. McConnell [33] was found to be a source of heterogeneity, which was reduced after exclusion without a change in conclusions. There was inter-study heterogeneity in the analysis of surgical blood loss between the two groups and each study was excluded on a case-by-case basis. Unfortunately, we do not find which study is responsible for the elevated heterogeneity. It may be the surgical skills and clinical experience of different surgeons that lead to the correlation rather than the final extracted data, thus we may not be able to find its source. In the above meta-analysis, we used a random effects model, and the results are considered reliable.

Conclusions

This study investigated the safety and efficacy of nHA matrix grafts and noHA grafts in spinal reconstruction. The results showed that the two regimens had similar clinical efficacy and safety. In addition, patients who underwent fusion with the nHA material had shorter surgery times and did not experience an increase in the amount of surgical bleeding or the incidence of risk events compared to the noHA graft group. There was no significant difference between the two groups in clinical outcomes in terms of VAS and ODI scores. The nHA matrix graft is an ideal alternative to inter-vertebral support bone grafts. However, the results may be biased due to the different clinical design types, aetiology and spinal surgery segments included in the study. Additional large-sample, multi-center, high-quality clinical trials should be encouraged to further validate the safety and efficacy of nHA matrix graft in spinal reconstruction.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12891-023-06405-x.

> **Additional file 1: Supplementary table.** The Meta-Analysis Literature Search Strategy (PubMed).

Authors' contributions
Kui Zhang: Writing-Original Draft; Yandong Zhu: Conceptualization, Project administration; Wenji Wang: Writing—Review & Editing, Supervision. The author(s) read and approved the final manuscript.

Availability of data and material
Our raw data are presented in the supplementary file. The datasets used and/or analysed during the current study available from the corresponding author (Wenji Wang) on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Zhang *et al. BMC Musculoskeletal Disorders*   (2023) 24:427

Page 10 of 11

References
1. Shi L, Ding T, Shi Y, et al. Comparison of the Outcomes of Minimally Invasive Transforaminal Lumbar Interbody Fusion and Endoscopic Transforaminal Lumbar Interbody Fusion for Lumbar Degenerative Diseases: A Retrospective Matched Case-Control Study. World Neurosurg. 2022;167:e1231–40.
2. Li P, Huang Y, Liang Z, et al. Clinical efficacy and therapeutic value of delayed surgery in patients with symptomatic old thoracolumbar fractures. BMC Surg. 2021;21:1–10.
3. Zhong W, Liang X, Luo X, et al. Imaging evaluation of nano-hydroxyapatite/polyamide 66 strut in cervical construction after 1-level corpectomy: a retrospective study of 520 patients. Eur J Med Res. 2020;25(1):1–8.
4. Hu B, Yang X, Hu Y, et al. The n-HA/PA66 cage versus the PEEK cage in anterior cervical fusion with single-level discectomy during 7 years of follow-up. World Neurosurg. 2019;123:e678–84.
5. Ngo J, Mousselli M, Lee Y P. Cage and Graft Options in Lateral Lumbar Interbody Fusion[C]//Seminars in Spine Surgery. WB Saunders, 2022: 100943.
6. Goldberg J L, Meaden R M, Hussain I, et al. Titanium versus polyetheretherketone versus structural allograft in anterior cervical discectomy and fusion: A systematic review. Brain Spine. 2022;2:100923.
7. Park JB, Yang JH, Chang DG, et al. Comparison of union rates between autogenous iliac crest bone graft and local bone graft as fusion materials in lumbar fusion surgery: an evaluation of up to 3-level fusion. World Neurosurg. 2020;139:e286–92.
8. Cottrill E, Premananthan C, Pennington Z, et al. Radiographic and clinical outcomes of silicate-substituted calcium phosphate (SiCaP) bone grafts in spinal fusion: Systematic review and meta-analysis. J Clin Neurosci. 2020;81:353–66.
9. Lee JH, Lee JH, Park JW, et al. Fusion rates of a morselized local bone graft in polyetheretherketone cages in posterior lumbar interbody fusion by quantitative analysis using consecutive three-dimensional computed tomography scans. Spine J. 2011;11(7):647–53.
10. Chen Y, Li X. The utilization of carbon-based nanomaterials in bone tissue regeneration and engineering: respective featured applications and future prospects. Med Novel Technol Devices. 2022;16:100168.
11. Lett JA, Sagadevan S, Fatimah I, et al. Recent advances in natural polymer-based hydroxyapatite scaffolds: Properties and applications. Eur Polymer J. 2021;148:110360.
12. Du M, Chen J, Liu K, et al. Recent advances in biomedical engineering of nano-hydroxyapatite including dentistry, cancer treatment and bone repair. Compos B Eng. 2021;215:108790.
13. Christy PN, Basha SK, Kumari VS, et al. Biopolymeric nanocomposite scaffolds for bone tissue engineering applications–A review. J Drug Deliv Sci Technol. 2020;55:101452.
14. Dimar JR, Glassman SD, Burkus JK, et al. Clinical and radiographic analysis of an optimized rhBMP-2 formulation as an autograft replacement in posterolateral lumbar spine arthrodesis. JBJS. 2009;91(6):1377–86.
15. Chen G, Yin M, Liu W, et al. A novel height-adjustable nano-hydroxyapatite/polyamide-66 vertebral body for reconstruction of thoracolumbar structural stability after spinal tumor resection. World Neurosurg. 2019;122:e206–14.
16. Neen D, Noyes D, Shaw M, et al. Healos and bone marrow aspirate used for lumbar spine fusion: a case controlled study comparing healos with autograft. Spine. 2006;31(18):E636–40.
17. Thomé C, Leheta O, Krauss JK, et al. A prospective randomized comparison of rectangular titanium cage fusion and iliac crest autograft fusion
in patients undergoing anterior cervical discectomy. J Neurosurg Spine. 2006;4(1):1–9.
18. Chang WC, Tsou HK, Chen WS, et al. Preliminary comparison of radiolucent cages containing either autogenous cancellous bone or hydroxyapatite graft in multilevel cervical fusion. J Clin Neurosci. 2009;16(6):793–6.
19. Dawson E, Bae HW, Burkus JK, et al. Recombinant human bone morphogenetic protein-2 on an absorbable collagen sponge with an osteoconductive bulking agent in posterolateral arthrodesis with instrumentation: a prospective randomized trial. JBJS. 2009;91(7):1604–13.
20. Deng Q, Ou Y, Zhu Y, et al. Clinical outcomes of two types of cages used in transforaminal lumbar interbody fusion for the treatment of degenerative lumbar diseases: n-HA/PA66 cages versus PEEK cages. J Mater Sci - Mater Med. 2016;27:1–9.
21. Cho JH, Lee JH, Yeom JS, et al. Efficacy of Escherichia coli-derived recombinant human bone morphogenetic protein-2 in posterolateral lumbar fusion: an open, active-controlled, randomized, multicenter trial. Spine J. 2017;17(12):1866–74.
22. Vonderhoeh NH, Voelker A, Heyde CE. Results of lumbar spondylodeses using different bone grafting materials after transforaminal lumbar interbody fusion (TLIF). Eur Spine J. 2017;26:2835–42.
23. Rickert M, Fleege C, Papachristos I, et al. Clinical outcome after anterior lumbar interbody fusion with a new osteoinductive bone substitute material. Clin Spine Surg. 2019;32(7):E319–25.
24. Cakir T, Yolas C. Synthetic bone graft versus autograft obtained from the spinous process in posterior lumbar interbody fusion[J]. Turk Neurosurg. 2021;31(2):199–205.
25. Yoshii T, Hashimoto M, Egawa S, et al. Hydroxyapatite/collagen composite graft for posterior lumbar interbody fusion: a comparison with local bone graft[J]. J Orthop Surg Res. 2021;16:1–8.
26. Zhu C, He M, Mao L, et al. Titanium interlayer-mediated hydroxyapatite-coated polyetheretherketone cage in transforaminal lumbar interbody fusion surgery[J]. BMC Musculoskelet Disord. 2021;22(1):1–8.
27. Korovessis P, Koureas G, Zacharatos S, et al. Correlative radiological, self-assessment and clinical analysis of evolution in instrumented dorsal and lateral fusion for degenerative lumbar spine disease. Autograft versus coralline hydroxyapatite. Eur Spine J. 2005;14:630–8.
28. Chen W, et al. Effectiveness of polyaminoacid/nano-hydroxyapatite/calcium sulfate cage for lumbar interbody fusion in patients with lower lumbar degenerative diseases: a mid-term study. Chin J Bone Joint Surg. 2020;13:22–7.
29. Liang X, Zhong W, Quan Z, et al. Clinical effect of the nano-hydroxyapatite/polyamide66 cage in reconstruction of cervical stability: a midterm follow-up study. Chin J Spine Spinal Cord. 2018;28:297–302.
30. Liu XH, et al. Initial curative effect comparision of ano-hydroxyapatite polyamide-66 cage and polyetheretherketone cage on anterior cervical intervertebral disc discectomy and fusion. Chin J Clin Anat. 2012;30:687–92.
31. Ma L, et al. Poly amino acid / nano hydroxyapatite / calcium sulfate interbody fusion cage Calcium sulfate interbody fusion cage. Chin J Reparative Reconstr Surg. 2016;30:328–35.
32. Delécrin J, Takahashi S, Gouin F, et al. A synthetic porous ceramic as a bone graft substitute in the surgical management of scoliosis: a prospective, randomized study[J]. Spine. 2000;25(5):563–9.
33. McConnell JR, Freeman BJC, Debnath UK, et al. A prospective randomized comparison of coralline hydroxyapatite with autograft in cervical interbody fusion. 2003.
34. Mondal S, Pal U. 3D hydroxyapatite scaffold for bone regeneration and local drug delivery applications. J Drug Deliv Sci Technol. 2019;53:101131.
35. Venkatesan J, Kim SK. Nano-hydroxyapatite composite biomaterials for bone tissue engineering—a review. J Biomed Nanotechnol. 2014;10(10):3124–40.
36. Ji Y, Wang M, Liu W, et al. Chitosan/nHAC/PLGA microsphere vehicle for sustained release of rhBMP-2 and its derived synthetic oligopeptide for bone regeneration. J Biomed Mater Res, Part A. 2017;105(6):1593–606.
37. Bharadwaz A, Jayasuriya AC. Recent trends in the application of widely used natural and synthetic polymer nanocomposites in bone tissue regeneration. Mater Sci Eng, C. 2020;110:110698.

Zhang *et al. BMC Musculoskeletal Disorders*   (2023) 24:427

Page 11 of 11

38. Gao Y, Li J, Cui H, et al. Comparison of intervertebral fusion rates of different bone graft materials in extreme lateral interbody fusion. Medicine. 2019;98(44):e17685.
39. Huang H, Liu J, Wang L, et al. A critical review on the biomechanical study of cervical interbody fusion cage. Med Novel Technol Devices. 2021;11:100070.

Publisher's Note