Bioactive Materials 10 (2022) 474–491

Contents lists available at ScienceDirect

Bioactive Materials

journal homepage: www.sciencedirect.com/journal/bioactive-materials

Evaluation of patches for rotator cuff repair: A systematic review and meta-analysis based on animal studies

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ARTICLE INFO

Keywords:
Rotator cuff patch
Animal model
Systematic review
Meta-analysis
Safety and effectiveness

ABSTRACT

Based on the published animal studies, we systematically evaluated the outcomes of various materials for rotator cuff repair in animal models and the potentials of their clinical translation. 74 animal studies were finally included, of which naturally derived biomaterials were applied the most widely (50.0%), rats were the most commonly used animal model (47.0%), and autologous tissue demonstrated the best outcomes in all animal models. The biomechanical properties of naturally derived biomaterials (maximum failure load: WMD 18.68 [95%CI 7.71–29.66]; P = 0.001, and stiffness: WMD 1.30 [95%CI 0.01–2.60]; P = 0.048) was statistically significant in the rabbit model. The rabbit model showed better outcomes even though the injury was severer compared with the rat model.

1. Introduction

Rotator cuff is a group of muscles that wrap around the humeral head to maintain mobility and stability of the humeral glenoid joint [1]. When a shoulder joint is undergoing degenerative change or trauma, rotator cuff injury happens, resulting in pain, stiffness, reduced functionality and mobility of the shoulder joint [2], which is the most common musculoskeletal disease second only to low back pain and neck pain [3–5]. More than 30 million people worldwide [6] and 17 million people in the United States [7] suffered from rotator cuff injuries every year. 250,000 patients received rotator cuff repair surgery annually, with an estimated cost of US $3 billion [8,9].

The tendon-bone healing process after the surgery is dynamic, involving inflammation, restoration and tissue remodeling, and the outcome depends on the interaction between the fibroblasts in the tendon tissue layers and the osteoblasts and collagens in the bone layers [10]. For patients with symptoms and large-area rotator cuff injury, since non-surgical treatment cannot achieve satisfactory results [11], surgery has become the first choice. Arthroscopic surgery is regarded as the "gold standard" to treat rotator cuff injury due to its advantages including smaller incisions and fewer complications [12]. However, for patients with large-area rotator cuff injury, factors including injury area [13], patient age [14], injury time [15], tendon quality [16], tendon atrophy and fatty infiltration [17–19], as well as removal of suture anchor after surgery, rupture of suture materials, slippage of surgical knot, tendon cutting, or tears in a new position [20,21] may cause problems in the tendon-bone interface, such as difficulty in healing or formation of fibrovascular scar tissue interface. As a result, the new fibrous vascular tissue lacks the gradient mineral distribution and continuity of collagen fiber [22], and cannot recover to the original tissue structure and biomechanical properties, leading to the failure rate of rotator cuff repair between 20% and 95% [2,23,24]. Although different repair

Peer review under responsibility of KeAi Communications Co., Ltd.
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https://doi.org/10.1016/j.bioactmat.2021.08.016
Received 14 July 2021; Received in revised form 12 August 2021; Accepted 12 August 2021
Available online 28 August 2021

strategies, fixation schemes and postoperative rehabilitation methods have been used [25–28], it still remains a great clinical challenge to reduce the failure rate of rotator cuff repair. Given the limited healing ability and high repair failure rate, improving the biological characteristics of the repaired site of rotator cuff is considered to be an effective approach [29].

In recent years, tissue engineering has emerged as a potential solution for soft tissue repair. It aims to improve the interaction between cells, to construct extracellular matrix scaffold, and to promote the growth factors required for tissue regeneration [30]. The ideal rotator cuff patches should have the characteristics of biodegradability, safety, easy operation and storage. At present, there are five types of rotator cuff patches: non-degradable synthetic materials, degradable synthetic materials, autologous tissue, allogeneic tissue and naturally derived biomaterials. Synthetic materials such as polyester [31,32] and polylactic acid (PLA) patches [33,34] have good mechanical strength as a carrier [35,36], but they may cause serious chronic inflammation and immune reaction after surgery [37,38]. Naturally derived biomaterials, such as collagen [39,40], dermal extracellular matrix [41,42] and fascia lata [43,44], have less rejection reaction and better biological activity, but poor mechanical properties, elasticity and toughness [35,45,46]. In addition, there is no consensus and clear guidelines on the safety and performance of repair materials as well as the mechanism of action [47,48].

Animal model is the main translational approach for studying the mechanism of action, effectiveness and safety of medical products in tissue engineering and regenerative medicine. In the past decades, animal model has been widely used to study rotator cuff repair strategies [49], meanwhile new materials must be fully verified in animal studies before clinical trials and clinical application [50]. At present, some animal experiments have been done to study the biomechanical properties and effect of rotator cuff patches, but there are still some limitations [51]. For example, there are some contradictions in the results of safety and effectiveness [52–54]. Therefore, it is necessary to conduct a systematic and comprehensive analysis on all the published animal studies of rotator cuff patches to date regarding their safety and effectiveness through scientific methods, which will provide references and supporting evidence for subsequent animal studies and clinical translation of rotator cuff patches [55].

Systematic review is a method of literature synthesis that comprehensively and extensively collects, screens and evaluates all relevant research evidence in this field for a specific issue of scientific research, and conducts quantitative comprehensive analysis (i.e., meta-analysis) on the included data from different studies [56–59]. Compared with the traditional review, the systematic review carried out by scientific methods can evaluate all the current relevant research evidence more objectively and provide a more accurate evaluation of the outcomes, which is regarded as the highest level of evidence in medical research [60,61]. Although a large number of animal experiments have been conducted on different types of rotator cuff patches in the early stage of clinical translation, it is still blank in the field evidence-based research for this topic at present.

The purpose of this study is to perform a retrospective analysis of patches for rotator cuff repair in the published animal experiments with the method of systematic review. It focuses on the analysis of research design, selection of patch, animal model, anatomical site, construction of a rotator cuff injury model, follow-up time, and histological and biomechanical results, etc. Furthermore, the safety and effectiveness of patches for rotator cuff repair have been also evaluated, which could provide theoretical guidance and references for future preclinical experimental research.

2. Materials & methods

2.1. Purpose

The purpose of this study is to systematically review and evaluate the effect of patches for rotator cuff repair in animal experiments.

2.2. Quality assurance

This study was carried out with reference to the process of *Cochrane Handbook for Systematic Reviews of Intervention* [62] and the PRISMA checklist of the review was provided as Appendix 1. The participants were trained with PICOS of this study (P: specific patient or population; I: intervention; C: comparison/control; O: outcome. S: study design), inclusion and exclusion criteria, literature screening and data extraction process, evaluation criteria of GRADE and GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative Research) evidence quality assessment tools, and interpretation and evaluation principles of the assessment tools of risk of bias in animal experiments based on SYRCLE. After the training, Kappa test was used for consistency examination. 10% of the literature was randomly selected for preliminary screening. When Kappa value $\geq$ 0.8, the training was qualified, and we started the study.

2.3. Inclusion and exclusion criteria

The PICOS was developed in strict accordance with the research design. The title, abstract and full text of each included literature were carefully examined to extract the required data. Only animal studies that met the following criteria were included in the final systematic review and meta-analysis.

2.3.1. Population

Animal models of rotator cuff injuries, without limit to animal species or modeling methods

2.3.2. Intervention

It was required to be repaired by patches. There was no restriction on the types of materials and repair methods, or on the addition of cells/factors either.

2.3.3. Comparison/control

1) Repairing the injury by simple surgical suture of the tendon-tendon or tendon-bone interface without patches; 2) Repairing the injury by patches.

2.3.4. Measurement indicators

1) Indicators related to histological repair: Collagen fibers formed, without limit to the histological staining methods.
2) Indicators related to biomechanical test: ① The maximum failure load, i.e., the maximum load at tendon fracture; ② Stiffness, i.e., calculated according to the load-displacement curve.

As included in the study of different animal species, including rats, rabbits, sheep, and dogs, there were certain differences between tendon-bone interface healing time of the rotator cuff injury. In order to facilitate the combined analysis of the indicators, this systematic review analyzed the studies included with the follow-up time of each animal species and the corresponding outcomes combined.

2.3.5. Research type

Randomized, controlled, or self-controlled experiments.

2.4. Search strategies

We retrieved the required data from PubMed (construction until November 2020) and Ovid-Embase (1974 to November 2020). At the same time, the references included in the study were also examined, and the relevant authors were contacted to provide the required information if the published data were not complete. The retrieval method combined the medical subject heading (MeSH) words and free words. Table 1 presents the search strategies in PubMed. See Appendix 2 for the detailed search strategies for the English literature.

2.5. Literature screening and data extraction

Four qualified researchers (Jinwei Yang, Yanbiao Jiang, Bing Zhao and Mingyue Jiao) independently screened the literature and extracted the data in strict accordance with the inclusion and exclusion criteria, and cross-checked the data. In case of divergence, a third party (Bin Ma) would make the decision. According to the pre-established table of full-text data extraction, the content extracted consisted of: 1) Basic parameters: including experimental animal species, gender, age, weight, sample size, injured part of rotator cuff, injury type, damage degree, repair methods, patch type and specifications, and follow-up time. 2) Outcome indicators: ① Histological indicators: collagen fiber formation; ② Biomechanical indicators: maximum failure load and stiffness.

2.6. Assessment of risk of bias

Based on the SYRCLE's assessment tool of risk of bias in animal experiments [64], two trained and qualified researchers (Yuhao Kang, Jia Jiang) independently assessed and cross-checked the inherent risk of bias of all included studies, including ten items in six aspects: selectivity bias, implementation bias, measurement bias, follow-up bias, reporting bias and others. If there was any objection, it would be decided through negotiation with a third party (Jinzhong Zhao). "Yes" means low risk of bias, "no" means high risk of bias, and "uncertain" means uncertain risk of bias.

2.7. Assessment of evidence quality

Whether the results of systematic review of animal experiments can be translated into clinical trials is closely related to the quality of evidence included in the study. According to the evidence grading evaluation tool of GRADE-CERQual qualitative systematic review supported and developed by the Cochrane Collaboration [65,66], qualitative indicators were applied to assess the quality of evidence from the following four aspects: 1) Methodological limitation; 2) Correlation; 3) Consistency of results; 4) Adequacy of data. Firstly, the above four aspects were evaluated separately, and finally, the overall quality of evidence was obtained by integrating the evaluation results of each part [66]. Based on GRADE evidence grading system [67], quantitative indicators were used to assess the evidence quality in the following five aspects: 1) Research limitation; 2) Inconsistency of results; 3) Indirectness; 4) Inaccuracy; and 5) Publication bias. First of all, the evidence quality of each result was evaluated, and then the evaluation results of each part were integrated to achieve the grades of evidence: high, medium, low and extremely low.

Table 1
Search strategies in PubMed.

Search subject	Keywords	Results
#1 Type of study	"Rotator Cuff Injuries" [Mesh] OR "Rotator Cuff Tear Arthropathy" [Mesh] OR "Rotator Cuff" [Mesh] OR Rotator Cuff [Title/Abstract] OR supraspinatus [Title/Abstract] OR infraspinatus [Title/Abstract] OR subscapularis [Title/Abstract] OR teres minor [Title/Abstract] OR shoulder pain [Title/Abstract] OR shoulder injur*[Title/Abstract]	22453
#2 Object of study	Search filter for animal experimentation developed by Hooijmans et al. [63]	7169286
#3 Exclusion	"letter" [publication type] OR "comment" [publication type] OR "editorial" [publication type] OR review [publication type]	4597526
#4 Combination of all	(1 and 2) not 3	1285

2.8. Statistical analysis

The quantitative data were statistically analyzed using Stata 15.0. Weighted mean difference (WMD) was used as statistic for effect analysis of biomechanical indicators (maximum failure loads and stiffness of biodegradable synthetic materials, autologous tissues and naturally derived biomaterials in rat or rabbit models, respectively) related to tendon-bone healing as continuous measurement data. The heterogeneity among the included results was analyzed by $\chi 2$ test ($\alpha = 0.1$), and the magnitude of heterogeneity was quantitatively determined by I^2. If there was no statistical heterogeneity among the results, a fixed-effect model was used for meta-analysis. Otherwise, the sources of heterogeneity were further analyzed, and the random effect model was used for meta-analysis after excluding the factors that significantly affected the clinical heterogeneity. The test level was set as $\alpha = 0.05$. If there was significant heterogeneity among studies, subgroup analysis, sensitivity analysis and other methods were used, or only qualitative and descriptive analysis was conducted. Funnel plots and Egger's test were used to evaluate publication bias.

3. Results

3.1. Search results

A total of 4697 articles were obtained in the preliminary examination, among which 837 duplicate articles were excluded. After reading the title and abstract of 3860 articles, 3270 articles were excluded. After reading the full text of 590 articles that might meet the requirements, 364 articles without patch repair, four articles without specific rotator cuff injury modeling information, 67 articles without rotator cuff injury model, 62 without in vivo experiments, 14 without full text and five duplicate literatures were excluded, and 74 articles with animal experiments that met the requirements were finally included. The detailed results of screening full text were in Appendix 3. The PRISMA screening flow chart is shown in Fig. 1.

The 74 studies finally included were from 11 countries including the United States, China and Japan, and published between 2001 and 2020, especially frequently in recent five years (2015–2020) (Fig. 2). Four different animal species were used in the included studies, including rats (35 studies), rabbits (22 studies), sheep (10 studies), and dogs (seven studies). Most of the included studies (77.0%) used small animal models to explore the histological results and biomechanical properties. The most commonly used methods to evaluate the results of rotator cuff repair were histological staining (97.3%) and biomechanical test (81.1%). Due to the different evaluation methods and great heterogeneity, as well as qualitative description of histological results, only descriptive analysis was conducted, and the meta-analysis of biomechanical indicators (quantitative data) was performed.

3.2. Basic characteristics of the included studies

The 74 studies included five types of materials, including three studies on non-degradable synthetic materials, 21 on degradable synthetic materials, 11 on autologous tissue, four on allogeneic tissue, and 39 on naturally derived biomaterials. The proportion of each material is shown in Fig. 3 a. Based on the research of the five materials in animal models, we summarized the information of the dominating naturally

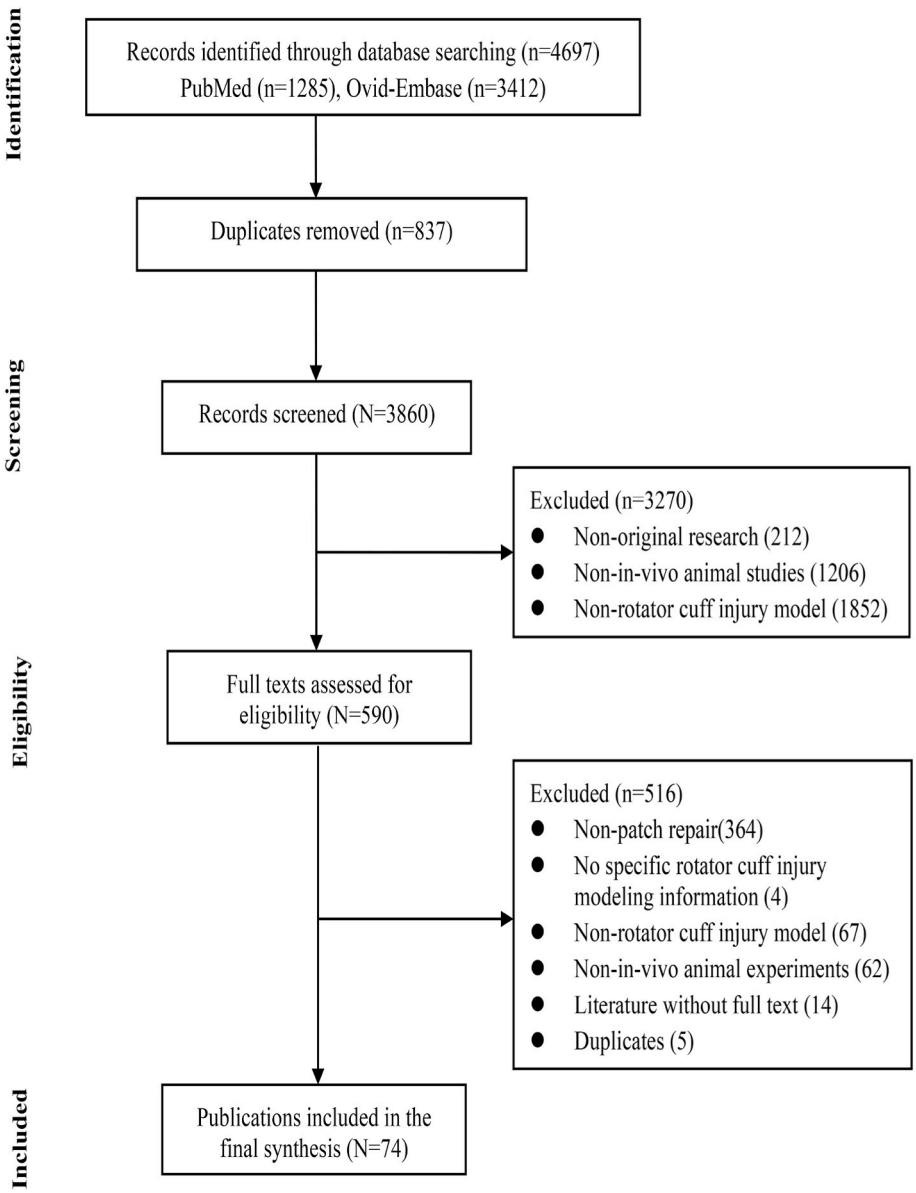

Fig. 1. PRISMA flow diagram for the systematic search.

derived biomaterials (50.0%) including design type, animal gender, age, weight range, sample size, follow-up time, site and degree of injury, and other basic information in Table 2, and the rest of the basic information regarding other materials is shown in Appendix 4. The histological results of all patches can be found in Appendix 5. Rats are the most common species in the animal models of rotator cuff injury, and the proportion of animal species used in this study and the frequency of rotator cuff injury types of each animal species are shown in Fig. 3 b. The repairing methods of rotator cuff injury include patch augmentation (41.9%), bridging (43.2%) and interposition (14.9%).

3.3. Histological results

3.3.1. Non-biodegradable synthetic materials

Two studies discussed the histological results of the non-biodegradable materials for rotator cuff repair. One [102] was on polycarbonate (polycarbonate-polyurethane) patches for supraspinatus tendon repair in rats. The results showed that the patch group has better efficacy than the simple suture group six weeks after the surgery. The other study [103] used the non-biodegradable expanded polytetrafluoroethylene (ePTFE), polysiloxane (silicone), and the biodegradable sodium hyaluronate-carboxymethyl cellulose (SH-CMC) together to repair the rotator cuff tears of rabbits. After six weeks, it was observed that none of the three types of materials could prevent or reduce the postoperative fibrosis of the rotator cuff tears.

3.3.2. Biodegradable synthetic materials

21 studies investigated the histological results of biodegradable materials for rotator cuff repair. Among them, seven studies on polycaprolactone (PCL) scaffolds, four on PLA and poly (L-lactide) (PLLA) scaffolds, four on poly (lactic-co-glycolic) acid (PLGA) scaffolds, two on PLGA-PCL nano scaffolds, one on hydroxyapatite-gradient (HA-G) scaffolds, one on Poly (D, L-Lactide-Co-Glycolide) (PLG), one on Poly (85 lactic acid-co-15 glycolic acid) copolymer, and one on SH-CMC.

One study [104] found the efficacy of PCL was better than simple suture. In two studies [105,106], factors were added to PCL scaffold, and the results of the added factor group were better than those of the bare scaffold group. PCL fiber processing or coating modification was performed in three studies. Kim, W [107] used restrictive processing on PCL material to produce “flat patch” and “tendon-inspired patch”, and the

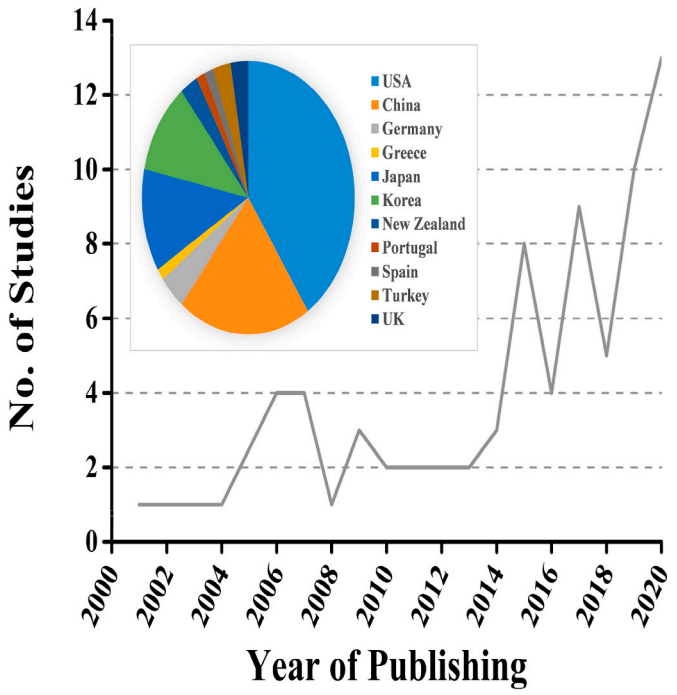

Fig. 2. Line chart representing the number of the published studies included in the systematic review sorted by the year of publishing. Inset graph for a pie chart represents the country affiliations of all the co-authors.

latter significantly improved the tendon-bone healing. Cong, S [108] used nonaligned PCL (nPCL)-Collagen II and nPCL-nanohydroxyapatite (nHA) electrospun layer by layer to the end of aligned PCL (aPCL)--Collagen I, and the tendon maturity score of the electrospun scaffold group was higher. Willbold, Elmar [109] used a chitosan-polycaprolactone graft copolymer to coat PCL, and the results were better in the coated PCL group than in the bare PCL scaffold group.

Three studies discussed the results of PLA and PLLA scaffolds. Two studies [110,111] compared the results of PLLA scaffolds with simple suture, and the efficacy of the former was better than that of the latter. Zhao, S [112] grafted gelatin on PLLA scaffold to form Gelatin-PLLA, which significantly increased collagen content at the tendon-bone interface. MacGillivray, J. D [113] discussed the comparison between PLA and simple suture, and found that PLA was not conducive to the healing of tendon-bone interface.

Four studies added different components on the PLGA scaffolds, among which one study [114] reported the addition of ibuprofen could control the release of drugs and promote the reconstruction of tendon tissue. Zhao, S [32] added basic fibroblast growth factor (bFGF) to the scaffold, and found that the added factor group had better results than the factor free scaffold group. Su, W [115] mixed the PLGA scaffold with graphene oxide (GO), which promoted more new bone formation and cartilage than the pure PLGA group. Lipner, J [116] investigated the results of PLGA adding bone morphogenetic protein-2 (BMP-2) factor and found that the tendon-bone interface was dominated by fibrous scar, suggesting that BMP-2 factor was not conducive to the healing of tendon-bone interface.

Sun, Y [117] discussed the comparison between electrospun PLGA/collagen I- PCL/nHA (PLGA/Col-PCL/nHA) and PLGA-PCL nano scaffolds. The former scaffold significantly promoted new bone formation and tissue regeneration. Tarafder, S [118] added multiple factors to PLGA-PCL scaffold, and the outcomes of the adding factor group were

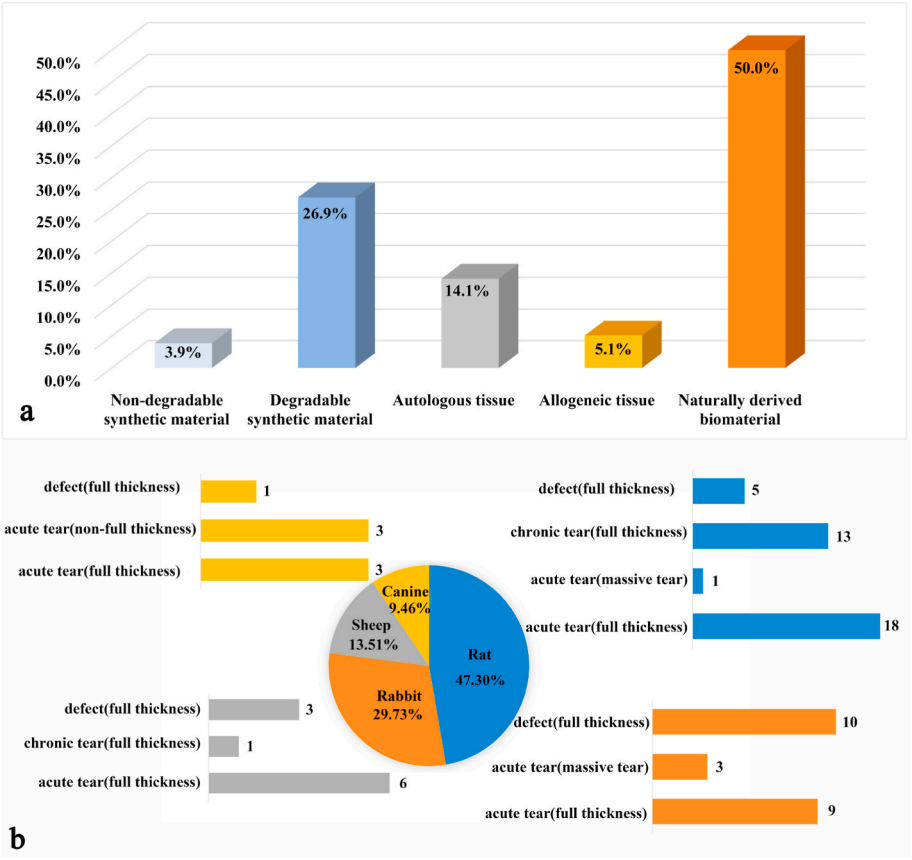

Fig. 3. a. Material types and proportions of rotator cuff patches; b. Animal models of rotator cuff injuries and the injury types and degrees.

Table 2
Characteristics of included animal studies (naturally derived biomaterials).

Author and year	Country	Model	Study design	Sample size (T/C)	Model	Types (degree)	Histological follow-up time	Biomechanical follow-up time
Baker, A. R 2012 [33]	USA	Canine (M, 23–28 kg, 9–13 Mos.)	Self-con	11/11	IS	Acute tear (non-full thickness)	12 WKS	12 WKS
Chung, S. W 2013 [68]	Korea	Rabbit/NZW (M, 3.5–4.0 kg, Mature)	Self-con	20/20	SS	Chronic tear (full thickness) (6 WKS)	4, 8 WKS	8 WKS
Dejardin, L. M 2001 [69]	USA	Dog (30–35 kg, Adult)	Self-con	16/16	IS	Defect (full thickness) (~20 mm)	3 Mos. 6 Mos.	3 Mos. 6 Mos.
Harada, Y 2017 [70]	Japan	Rat (Mean weight 250g, 12 WKS)	Self-con	30/30	IS	Acute tear (full thickness)	1 WKS	8 WKS
Hee, C. K 2011 [71]	USA	Ovine (F, 65–105 kg, 3.5+Years)	Self-con	60/60	IS	Acute tear (full thickness)	12 WKS	12 WKS
Huang, C 2020 [22]	China	Rabbit/NZW (F, 2.8–3.5 kg, Adult)	Ran	18/18	SS	Acute tear (full thickness)	4, 8, 12 WKS	4, 8, 12 WKS
Huang, C 2020 [72]	China	Rabbit/NZW (2.8–3.5 kg, Adult)	Self-con	24/24	SS	Acute tear (full thickness)	4, 8 WKS	4, 8 WKS
Kim, D. H 2019 [73]	Korea	Rat/SD (M, 300–350 g, 12 WKS)	Ran	20/20	SS	Acute tear (full thickness)	6, 12 WKS	6, 12 WKS
Kim, S. Y 2014 [74]	Korea	Rat/SD (M, 410–500 g, Adult)	Ran	19/19	SS	Acute tear (full thickness)	1, 2, 4, 8 WKS	2, 4, 8 WKS
Learn, G. D 2019 [75]	USA	Rabbit/NZW (F, 3–5 kg, 8–13 Mos.)	Con	6/5	IS	Acute tear (full thickness)	3 Mos.	3 Mos.
Zhu, M 2019 [39]	New Zealand	Rat/SD (More than 350 g, Older than 12 WKS)	Ran	20/20	SS	Acute tear (full thickness)	6, 12 WKS	6, 12 WKS
Schlegel, T. F 2006 [76]	USA	Sheep	Ran	13/13	IS	Acute tear (full thickness)	12 WKS	12 WKS
Kovacevic, D 2015 [40]	USA	Rat/SD (M, Mature)	Ran	19/19	SS	Acute tear (full thickness)	5, 28 Days	5, 28 Days
Lee, K. W 2017 [77]	Korea	Rabbit/NZW (M, 3.0 kg, 5 Mos.)	Con	12/12201	SS	Chronic tear (full thickness) (4 WKS)	4, 8 WKS	4, 8 WKS
Lopiz, Y 2017 [78]	Spain	Rat/SD (M, 480–850 g, 8 Mos.)	Con	10/10	SS	Chronic tear (full thickness) (16 WKS)	4 WKS	4 WKS
Omi, R 2016 [79]	USA	Rat/Lewis (F, Adult)	Con	11/11	SS	Acute tear (full thickness)	6 WKS	6 WKS
Pan, J 2015 [80]	China	Rabbit/NZW (M, 2.5–3.0 kg)	Ran	7/7	IS	Defect (full thickness)	4, 8, 12 WKS	4, 8, 12 WKS
Peterson, Dale R 2015 [81]	USA	Sheep (F, 50–80 kg, 2–4 Years)	Ran	10/10	IS	Acute tear (full thickness)	8, 26 WKS	8 WKS
Rodeo, S. A 2007 [82]	USA	Sheep (F, Mature)	Con	24/24	IS	Acute tear (full thickness)	6, 12 WKS	6, 12 WKS
Rothrauff, B. B 2019a [83]	USA	Rat/Lewis (M, Mature)	Con	12/6	SS; IS	Chronic tear (full thickness) (8 WKS)	4 WKS	4 WKS
Rothrauff, B. B 2019b [83]	USA	Rat/Lewis (M, Mature)	Con	12/6	SS; IS	Acute tear (full thickness)	4 WKS	4 WKS
Seeherman, H. J 2008 [84]	USA	Sheep (60–90 kg, 4–6 Years)	Self-con	10/13	IS	Acute tear (full thickness)	8 WKS	8 WKS
Smietana, M. J 2017a [85]	USA	Rat/Fisher 344 (F, 150–200 g)	Self-con	/	SS	Acute tear (full thickness)	8 WKS	8 WKS
Smietana, M. J 2017b [85]	USA	Rat/Fisher 344 (F, 150–200 g)	Self-con	/	SS	Chronic tear (full thickness) (4 WKS)	8 WKS	8 WKS
Funakoshi, T 2006 [86]	Japan	Rabbits/JW (3 kg)	Self-con	21/21	IS	Defect (full thickness) (~10 × 10 mm)	2, 4, 8, 12 WKS	4 WKS
Nicholson, G. P 2007a [87]	USA	Sheep (F, 80–110 kg, Adult)	Self-con	6/5	IS	Defect (full thickness)	9, 24 WKS	9, 24 WKS
Nicholson, G. P 2007b [87]	USA	Sheep (F, 80–110 kg, Adult)	Self-con	6/5	IS	Defect (full thickness)	9, 24 WKS	9, 24 WKS
Loeffler, B. J 2013 [88]	USA	Rat/Lewis (13.8 WKS)	Self-con	/	SS	Defect (full thickness) (~2 × 2 mm)	3, 6, 12 WKS	/
Nuss, C. A 2017 [89]	USA	Rat/SD (M, 400–450 g, Adult)	Ran	72/72	SS	Acute tear (full thickness)	2, 4, 8 WKS	4, 8 WKS
Thangarajah, T 2017a [90]	UK	Rat/Wistar (F)	Ran	6/6	SS	Chronic tear (full thickness) (3 WKS)	6 WKS	/
Thangarajah, T 2017b [90]	UK	Rat/Wistar (F)	Ran	6/6	SS	Chronic tear (full thickness) (3 WKS)	6 WKS	/
Tokunaga, T 2015 [91]	Japan	Rat/SD (M, 447.3 g ± 33.3 g, 19 to 21 WKS)	Ran	12/12	SS	Acute tear (full thickness)	2, 6, 12 WKS	12 WKS
Tokunaga, T 2017 [92]	Japan	Rabbit/JW (M, 3.25 ± 0.18 kg, Mature)	Ran	15/15	SS	Acute tear (full thickness)	12 WKS	12 WKS
Street, M 2015 [93]	New Zealand	Rat/SD (M, >350 g, >12 WKS)	Ran	12/12	SS	Acute tear (full thickness)	6, 12 WKS	6, 12 WKS
Thangarajah, T 2018 [94]	UK	Rat/Wistar (F)	Ran	6/6	SS	Chronic tear (full thickness) (3 WKS)	6 WKS	/
Adams, J. E 2006 [41]	USA	Canine (20–35 kg, >12 Mos.)	Self-con	30/19	IS	Acute tear (full thickness)	6 WKS, 3,6 Mos.	6 WKS, 3,6 Mos.
Ide, J 2009 [95]	Japan	Rat/SD (M, 501 ± 40 g)	Con	15/15	SS		2, 6, 12 WKS	2, 6, 12 WKS

(continued on next page)

Table 2 (*continued*)

Author and year	Country	Model	Study design	Sample size (T/C)	Model	Types (degree)	Histological follow-up time	Biomechanical follow-up time
						Defect (full thickness) (~3 × 5 mm)		
Kabuto, Y 2015 [96]	Japan	Rat/SD (M, 12WKS)	Self-con	15/15	SS	Defect (full thickness)	4, 8 WKS	4, 8 WKS
Liu, G. M 2018 [97]	China	Rabbit/NZW (2.5–3.0 kg)	Self-con	36/36	IS	Defect (full thickness) (~3 × 5 mm)	2, 4, 8 WKS	2, 4, 8 WKS
Qian, S 2019 [98]	China	Rabbit/NZW (F, 2.0–2.5 kg, 4 Mos.)	Ran	10/10	SS	Defect (full thickness) (~1 cm)	8, 12 WKS	/
Sevivas, N 2018 [99]	Portugal	Rat/Wistar	Ran	5/5	SS,IS	Chronic tear (full thickness) (16 WKS)	16 WKS	16 WKS
Smith, M. J 2020 [100]	USA	Canine (22 kg, 2–3Years)	Con	4/4	SS	Acute tear (non-full thickness) (~3–4 mm)	3,6 Mos.	3,6 Mos.
Zhang, X 2019 [101]	China	Rabbit/NZW (M, 2.5 kg, 16 WKS)	Self-con	36/36	SS	Defect (full thickness) (~10 × 10 mm)	4, 8, 12 WKS	4, 8, 12 WKS

F: female; M: male; Ran: random control; Con: control; Self-con: self-control; NZW: New Zealand White Rabbits; SD: Sprague-Dawley; Mos.: Months; WKS: Weeks; JW: Japanese white; SS: supraspinatus tendon; IS: infraspinatus tendon.

better than those of the bare scaffold group.

One study [119] investigated the tendon-bone healing results of adding umbilical cord-derived mesenchymal stem cells on the HA-G scaffold, and the results were better than those of the bare scaffold group. One study [120] investigated PLG scaffolds, which promoted collagen formation and had better outcomes than simple suture.

3.3.3. Autologous tissue

11 studies investigated the histological results of autologous tissue for rotator cuff repair, of which three studies on fascia lata autograft, two on periosteum autograft, two on tendon autograft, one on Achilles bursa autograft, one on bone-tendon composite autograft, one on free flexor tendon and patellar tendon-bone autograft, and one on stem cells from autologous urine.

Kataoka T [43] showed that the tendon maturity score of fascia lata autograft group was significantly higher than that of simple suture. McAdams, T R [121] investigated the fascia lata autograft combined with deltoid flap, and found that the content of collagen I was significantly increased in the combined deltoid flap group. Zhang, X [101] studied the results of autologous fascia lata and porcine small intestine submucosa, and found that the collagen fibers in the fascia lata group were more mature.

Two studies [122,123] included demonstrated that periosteum autograft group had better outcomes than simple tendon-bone suture. For tendon autograft, Liu, G. M [97] studied the comparison between autogenous tendon and multi-layer acellular tendon sheet, and there was no significant difference in the histological results between the two groups. Adams, J. E [41] discussed the comparison between tendon autograft and human acellular dermal matrix, and there was no significant difference in the histological results between the two groups.

Ficklscherer, A [124] found that comparing autologous Achilles tendon bursa tissue with simple suture, the former resulted in higher content of collagen II in the repaired site. Sun, Y [125] demonstrated that the bone-tendon composite autograft group had a higher tendon maturity score than simple suture. Chen, Y [126] discussed the stem cell sheets derived from urine of the patient, and the comparison with the tendon-bone suture showed that the cell sheet group presented more collagen fibers at the tendon-bone interface. Sener, M [127] compared the results between patellar tendon-bone autograft with free flexor tendon autograft, and found that the patellar tendon-bone autograft was completely integrated with the tibia.

3.3.4. Allogeneic tissue

Four studies investigated the results of allograft for rotator cuff repair. Novakova, S [128]. studied a scaffold free tissue-engineered tendon graft designed for rotator cuff repair, compared with the suture group, the graft group had more orderly collagenous fiber arrangement. Shin, M. J [129] investigated the results of adipose stem cell sheets and found that there was more fibrochondrogenic formation in the cell sheet group compared with the simple suture group. Varvitsiotis, D [130] studied allograft fascia lata and compared with simple suture, both groups showed fibroblast growth and collagen fibers at the tendon-bone interface without significant differences. Liu, Q [131] also studied the results of engineered tendon-fibrocartilage bone composite (TFBC) combined with bone marrow mesenchymal stem cells (BMSCs) sheet, and more collagen fibrous tissue formation was observed in the combined stem cell sheet group.

3.3.5. Naturally derived biomaterials

39 studies investigated the results of naturally derived biomaterials for rotator cuff repair. There were 10 studies on collagen sponge/scaffolds, 10 on extracellular matrix materials, five on gelatin hydrogel sheets (GHS), four on porcine small intestine submucosa (SIS), three on chitin, two on alginate scaffolds, and the others.

Zhu, M [39] found that the results were better in the collagen scaffold group than in the simple suture group. Two studies [40,71] added factors to the collagen scaffold, among which one [71] showed that the collagen scaffold in the factor-added group had better outcomes than the bare scaffold group, while Kovacevic, D [40] demonstrated that the results in both the patch group and the partially factor-added group were poorer than those in the simple suture group. Learn, G. D [75] added stem cells to the collagen scaffold, and there was no significant difference between the two groups. Qian, S [98] compared a random collagen scaffold combined with knitted silk (RCSS) and aligned collagen scaffold combined with knitted silk (ACSS), and the former has better results than the latter. Five studies collagen sponge for rotator cuff repair, among which four [81,82,84,88] had added factors to collagen sponge, and the results of the added factor group were better than those of the factor free collagen sponge group. One study [74] compared collagen sponge with Poloxamer 407, which showed that Poloxamer 407 had better results than collagen sponge.

Street, M [93] compared the ovine forestomach matrix scaffold with simple suture, more collagen fibers were formed in the former group. Thangarajah, T [94] investigated adding BMSCs to the demineralized cortical bone matrix, and found there was no difference between the two groups whether adding BMSCs or not. Another study by the same team [91] compared the demineralized cortical bone matrix with human dermal matrix scaffold, and there was no significant difference between the two groups. Smith, M. J [100] investigated amniotic matrix umbilical cord scaffold (AM), acellular human allograft (AF) and bovine collagen mesh (RMP), and the histological results of the AM and AF groups were better than those of the RMP and simple suture groups. For acellular tendon slices, Pan, J [80] found the acellular tendon sheet grafts had better results than simple suture. Omi, R [79] found more

collagen fibers were formed in the composite materials of tendon sheet than simple suture. Liu, G. M [97] found that there was no significant difference between multi-layer acellular tendon sheet and autologous tendon. For acellular dermal matrix grafts, two studies [77,95] added factors to the grafts, and the results of the group adding factors were better than those of the simple suture group. Adams, J. E [41] found there was no significant difference between human acellular dermal matrix and autologous tendon.

Three studies [91,92,96] demonstrated GHS adding factors had better results than factor free GHS group. Two studies investigated Gelatin methacryloyl (GelMA), of which the study of Huang, C [22] was loaded with Kartogenin (KGN) had better results than those of the factor free group. Another study [84] explored GelMA and fibrin hydrogel scaffolds with adipose-derived stem cells (ADSCs)/transforming growth factor-β3 (TGF-β3) loaded. Compared with the two kinds of hydrogel scaffolds, whether the supplementation of growth factor did not significantly improve the histological structure of tendon-bone interface.

Two studies [69,76] discussed SIS patches, and demonstrated that the SIS group had better results than simple suture. Nicholson, G. P [87] compared porcine SIS and porcine dermal patches, and found that the former had better results than the latter. Moreover, Zhang, X [101] compared porcine SIS and autologous fascia lata, and found that the fibers in the autologous fascia lata group were arranged more orderly.

Funakoshi, T [86] found the chitin source patches had better results than simple suture. Nuss, C. A [89] found that the results of Poly-N-acetyl Glucosamine (sNAG) were superior to those of simple suture. One study [73] demonstrated that alginate scaffolds had better results than simple suture. Lopitz, Y [78] found that alginate-chitin combined with recombinant human bone morphogenetic protein-2 (rhBMP-2) had better results than bare scaffolds. Sevivas, N [99] found the addition of BMSCs promoted the more formation of collagen fibers, which had better than bare keratin scaffolds.

3.4. Biomechanical properties

In this study, according to the material type and animal model, a meta-analysis was conducted on the maximum failure load and stiffness to reduce the heterogeneity between materials and species. Forest plot was used to display the number of included studies and analysis results. In the plane rectangular coordinate system, the vertical invalid line (abscissa scale zero) is regarded as the center; the multiple line segments in parallel to the horizontal axis refer to each confidence interval (CI), the blocks represent the effect size of each study, and the size of each block is proportional to the weight of each study; the merger results are represented by diamond, and the height of the diamond (the longest distance from the top to the bottom) refers to the point estimate, while the width of the diamond (the longest distance from the left to the right) refers to the confidence interval. When the 95% confidence interval contains zero, i.e. the horizontal line intersects with the invalid line, it means the experimental and the control groups have the equal outcome; if both the roof and the floor limits of the 95% CI are bigger than zero, i.e. the horizontal line is on the right of the invalid line, the outcome of the experimental group is better than the control group; if both the roof and the floor limits of the 95% CI are smaller than zero, i.e. the horizontal line is on the left of the invalid line, the outcome of the control group is better than the experimental group.

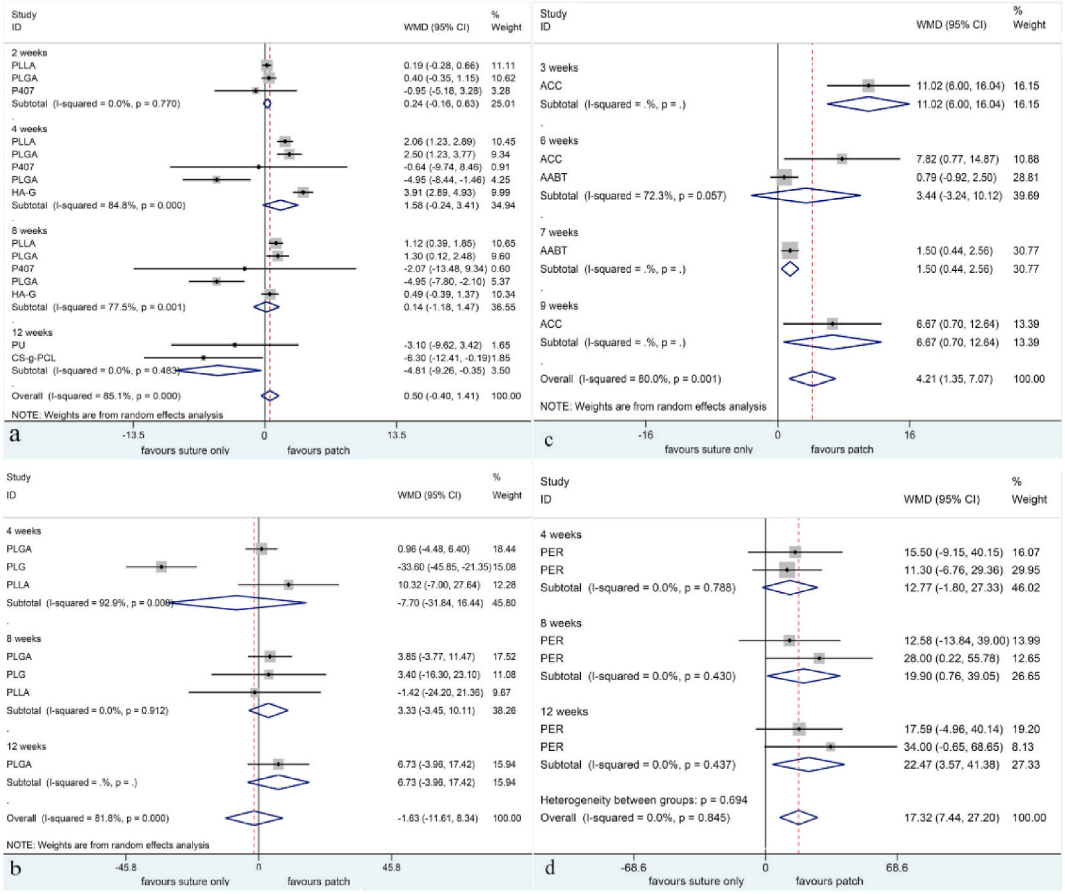

Fig. 4. Forest plot of the maximum failure load: a. biodegradable synthetic materials VS simple suture for rotator cuff repair (rat model); b. biodegradable synthetic materials VS simple suture for rotator cuff repair (rabbit model); c. autologous tissue VS simple suture for rotator cuff repair (rat model); d. autologous tissue VS simple suture for rotator cuff repair (rabbit model).

3.4.1. Maximum failure load

Of the 14 studies on biodegradable synthetic materials in the rat model (see Appendix 6), six studies were included in the meta-analysis. There was no significant difference in the maximum failure load between the biodegradable synthetic material and the simple suture groups (Fig. 4 a, WMD 0.50 [95%CI -0.40–1.41]; P = 0.275). The meta-analysis result showed the same maximum failure load in both groups. Three of the six studies on biodegradable synthetic materials in the rabbit model (see Appendix 6) were included in the meta-analysis. There was no significant difference in the maximum failure load between the biodegradable synthetic material and the simple suture groups (Fig. 4 b, WMD-1.63 [95%CI - 11.61–8.34]; P = 0.748). The meta-analysis result showed the same maximum failure load in both groups.

Both studies on autologous tissue in the rat model (see Appendix 7) were included in the meta-analysis. The maximum failure load of autologous tissue was statistically different from that of the simple suture group (Fig. 4 c, WMD 4.21 [95%CI 1.35–7.07]; P = 0.004). The result of meta-analysis showed that the maximum failure load of autologous tissue in the rat model was better than that of the control (simple suture) group. Two of the six studies on autologous tissue in the rabbit model (see Appendix 7) were included in the meta-analysis. The maximum failure load of autologous tissue was statistically different

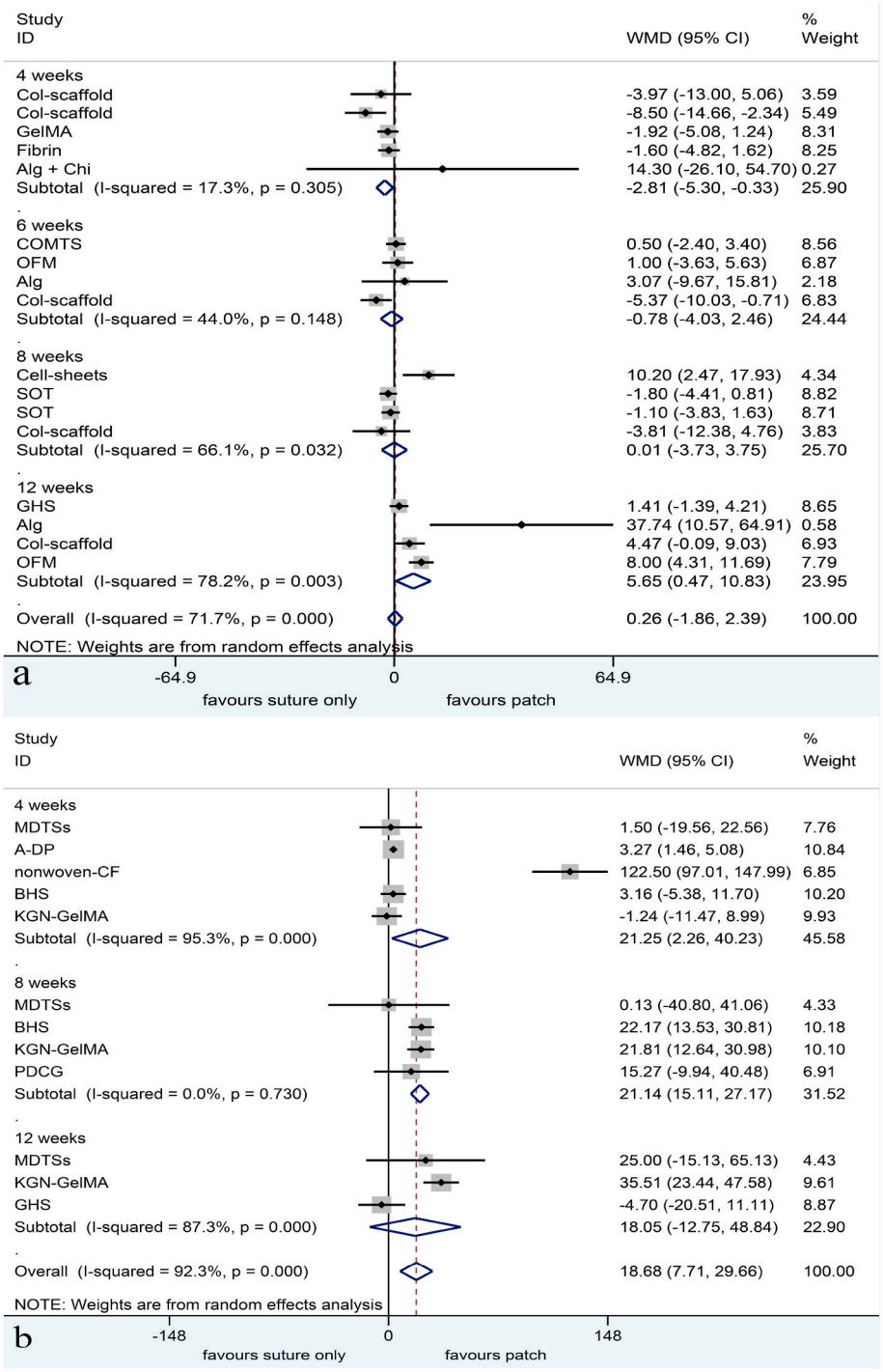

Fig. 5. Forest plot of the maximum failure load: a. naturally derived biomaterials VS simple suture for rotator cuff repair (rat model); b. naturally derived biomaterials VS simple suture for rotator cuff repair (rabbit model).

from that of the simple suture group (Fig. 4 d, WMD 17.32 [95%CI 7.44–27.20]; P = 0.001). The result of meta-analysis showed that the maximum failure load of autologous tissue in rabbit model was better than that of the control group.

11 of the 18 studies on naturally derived biomaterials in the rat model (see Appendix 8) were included in the meta-analysis. There was no statistical difference in the maximum failure load between the naturally derived biomaterials and the simple suture groups (Fig. 5 a, WMD 0.26 [95%CI - 1.86–2.39]; P = 0.807). The meta-analysis result showed the same maximum failure load in both groups. Seven of the 11 studies on naturally derived biomaterials in the rabbit model (see Appendix 8) were included in the meta-analysis. The maximum failure load of naturally derived biomaterials was statistically different from that of the simple suture group (Fig. 5 b, WMD 18.68 [95%CI 7.71–29.66]; P = 0.001). The meta-analysis result showed that the maximum failure load of naturally derived biomaterials in the rabbit model was better than that of the simple suture group.

3.4.2. Stiffnes

Of the 14 studies on biodegradable synthetic materials in the rat model (see Appendix 6), six were included in the meta-analysis. In the rat model, the stiffness of biodegradable synthetic material was statistically different from that of simple suture (Fig. 6 a, WMD 0.46 [95%CI 0.10–0.82]; P = 0.013). The meta-analysis result showed that the maximum failure load of biodegradable synthetic material in the rat model was better than that of simple suture. Three of the six studies on biodegradable synthetic materials in the rabbit model (see Appendix 6) were included in the meta-analysis. In the rabbit model, the stiffness of biodegradable synthetic materials was statistically different from that of simple suture (Fig. 6 b, WMD 0.74 [95%CI 0.19–1.30]; P = 0.008). The meta-analysis result showed that the stiffness of degradable synthetic material in rabbit model was better than simple suture.

Eight of the 18 studies on naturally derived biomaterials in the rat model (see Appendix 8) were included in the meta-analysis. In the rat model, there was no statistical difference in the stiffness between naturally derived biomaterials and simple suture (Fig. 6 c, WMD-0.02 [95%CI - 1.21–1.17]; P = 0.973). The meta-analysis result showed that the same stiffness in both the naturally derived biomaterials and the control groups in the rat model. Seven of the 11 studies on naturally derived biomaterials in the rabbit model (see Appendix 8) were included in the meta-analysis. In the rabbit model, the stiffness of naturally derived biomaterials was statistically different from that of the control group (Fig. 6 d, WMD 1.30 [95%CI 0.01–2.60]; P = 0.048). The meta-analysis result showed that the stiffness of naturally derived biomaterials was better than that in the control group in the rabbit model.

3.5. Publication bias

Funnel plot was drawn for the maximum failure load of biomechanical properties (rat model), as shown in Fig. 7, and Egger's test was conducted, as shown in Appendix 9. The results showed that almost all points located symmetrically within the funnel, and the result of Egger's test was P = 0.442 (P > 0.05), which means no publication bias.

3.6. Risk of bias and quality of evidence

The risk of bias was assessed by the SYRCLE's tool, and the result was shown in Fig. 8 and Appendix 10. Of the 74 animal studies included,

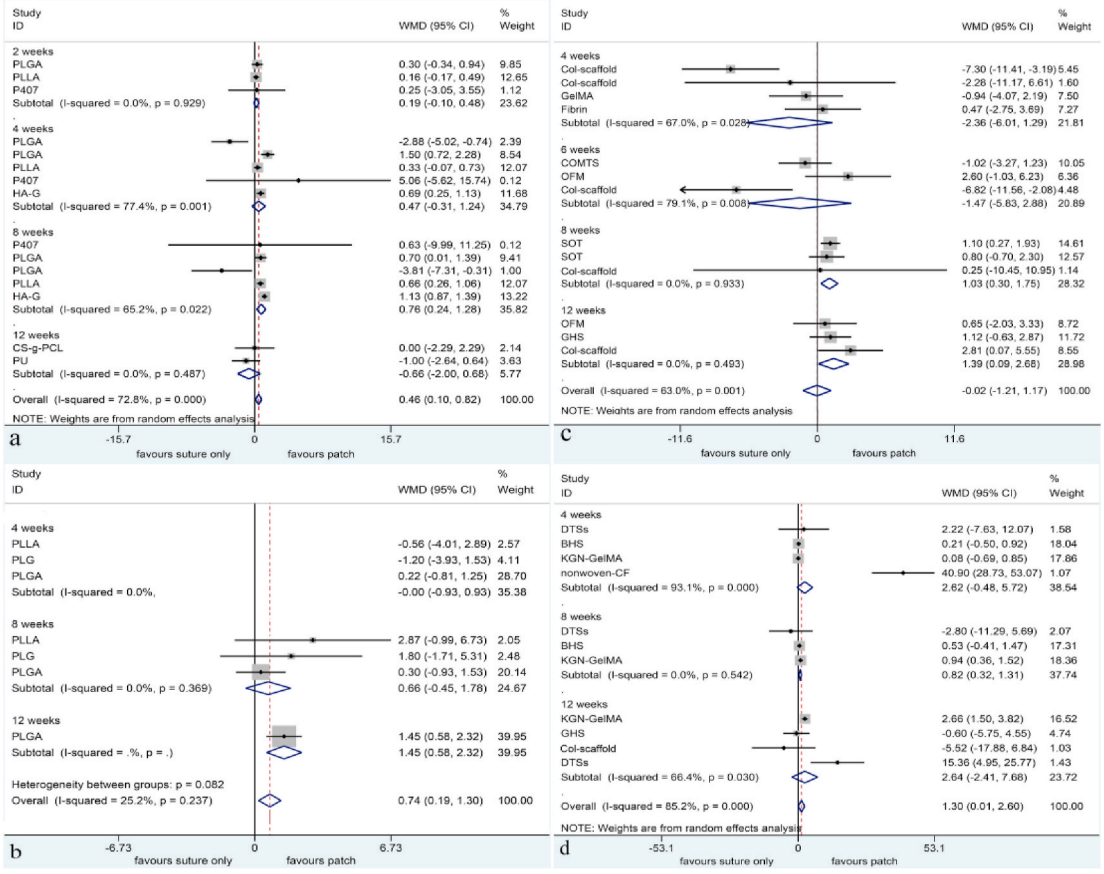

Fig. 6. Forest plot of stiffness: a. biodegradable materials VS simple suture for rotator cuff repair (rat model); b. biodegradable materials VS simple suture for rotator cuff repair (rabbit model); c. naturally derived biomaterials VS simple suture for rotator cuff repair (rat model); d. naturally derived biomaterials VS simple suture for rotator cuff repair (rabbit model).

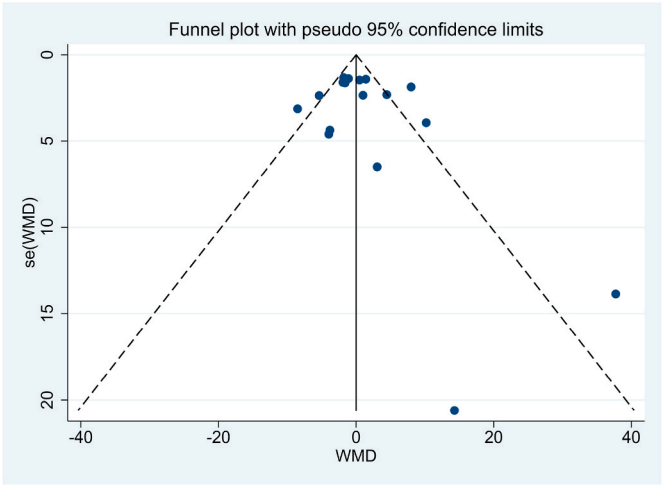

Fig. 7. Funnel plot of maximum failure load (rat model).

only 28 were randomized controlled studies, and three reported the method of random allocations, but only one of them applied allocation concealment. The baseline features of 26 studies were balanced, but none reported whether animal breeders and researchers were blinded. Only five studies randomized placement of laboratory animals. In 16 studies, animals were randomly selected for results evaluation. The evaluators of the results were blinded in 16 studies. Experimental animals from 52 studies were included in the final analysis. Although we did not have access to the research proposals, all expected results were clearly reported in the studies. For other sources of bias, 33 studies did not report funding or conflict of interest statements, and seven studies only analyzed animals that survived.

According to the assessment, the evidence quality of the three outcome indicators included in the study was all "low". The degradation of evidence quality were due to the poor methodological quality, indirect correlation, and clinical inconvertibility, as shown in Appendix 11.

4. Discussion

For the studies evaluating the materials to treat rotator cuff injuries, the majority are animal experiments, but the outcomes of different rotator cuff patches and the possibility of clinical transformation are not clear yet. In this systematic review, we observed the application of different types of rotator cuff repair materials in animal models. 74 studies were finally included for systematic review. We only did descriptive analysis on the experimental design methods, animal species, age, rotator cuff injury models, types of rotator cuff patches and evaluation criteria of outcome indicators and follow-up time because of their high heterogeneity; but did meta-analysis on the two quantitative data: the maximum failure load and stiffness, the indicators in the biomechanical test. Therefore, this systematic review was analyzed and discussed through a combination of qualitative description and quantitative analysis as to show the most appropriate animal model and the desired repair materials for rotator cuff injuries in the future.

4.1. Non-degradable synthetic materials for rotator cuff repair

Non-degradable synthetic materials can play a role of permanent support in rotator cuff repair. At present, such materials are rarely used in rotator cuff repair (only three studies were included), among which two studies showed that their histological and biomechanical results were better than the control. However, the results of one study on ePTFE [103] showed that it did not reduce postoperative fibrosis, but caused inflammation instead. This may be due to the non-degradable inert material and its surface characteristics, lack of good biocompatibility and easy to cause foreign body reaction. Although non-degradable materials have strong tensile strength, they may have certain long-term risks [132]. Due to their non-degradability and long-term retention in the body, they may produce foreign body reactions and cause repair failure. Therefore, it should be focused to reduce the foreign body reaction and improve the histocompatibility of these materials in the future.

4.2. Biodegradable synthetic materials for rotator cuff repair

Biodegradable synthetic materials are widely studied in the field of rotator cuff repair due to their good biocompatibility, degradability and particular mechanical strength [133] (21 studies were included). Our research showed that most of the studies on biodegradable synthetic materials demonstrated good histological and biomechanical properties when compared to simple tendon-bone suture. However, one study [116] showed that nano-scaffold materials had a negative effect on rotator cuff healing, which was attributed by the authors to inflammatory reaction, fibrovascularization, and bone loss caused by PLGA degradation related acidic microenvironment, and other reasons. The study of Inui, A [120] showed that the high concentration of lactic acid and glycolic acid released by the degradation of PLLA scaffold could affect the proliferation of tendon cells and osteoblasts, which was consistent with the studies of Meyer, F and Taylor, M.S [134,135]. A study [32] on PLGA showed that its metabolites could accumulate at the implant site and cause inflammation. At present, no relevant studies have shown how the biodegradable materials degrade at the tendon-bone interface and which degradation products will cause negative effect. Future studies should focus on the degradation mechanism of such materials and the means to control the degradation products in a safe range.

4.3. Autologous tissue for rotator cuff repair

Autologous tissue patch has good biocompatibility, and all the included studies showed that it did not cause inflammation. In terms of histological results, autologous tissue can better promote the healing of tendon-bone interface. In terms of biomechanical properties, the result of the meta-analysis showed that the maximum failure load in rat and

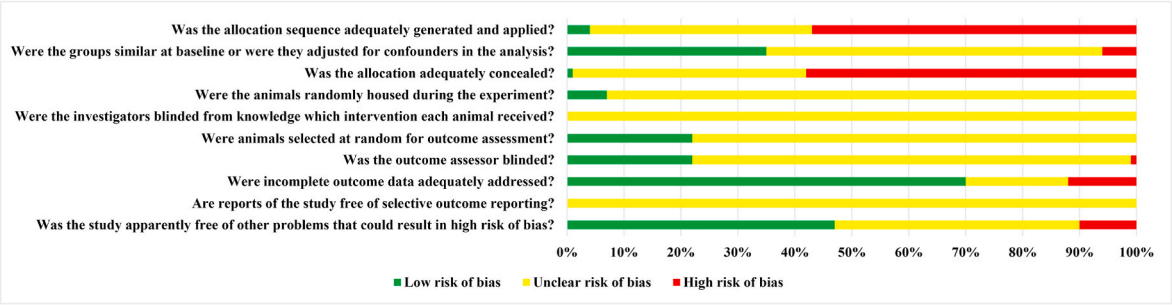

Fig. 8. Results of the risk of bias assessment of the 74 studies included in this systematic review.

rabbit models was better than that in the control. Therefore, autologous tissue may be the most promising choice for rotator cuff repair among all materials. The most commonly used autologous tissue, such as periosteum patch, contains a large number of blood vessels and multifunctional mesenchymal stem cells, whose differentiated chondrocytes and osteocytes play a positive role in promoting the tendon-bone healing process [136,137]. Meanwhile, the periosteum patch has bioactive substances such as TGF, BMP-2 and insulin-like growth factor, which contribute to the healing of tendon-bone interface. In the literature included in this study, in addition to autologous periosteum, tendon, fascia lata, and other autografts can promote tendon-bone healing, which can be used as one of the control criteria for animal test evaluation before clinical trials of the materials, and provide a certain experimental reference for the translation from animal experiment to clinical practice.

4.4. Allogeneic tissue for rotator cuff repair

Compared with simple tendon-bone suture, most studies have shown that allogeneic tissue can improve the histological results and enhance the biomechanical properties after rotator cuff injury. Allogeneic fascia lata, patellar tendon and tendon tissue are easy to obtain, and can be used to repair rotator cuff injuries. Host cells can be induced to proliferate into the structure, and generate the components of new extracellular matrix, regenerating new tissue. However, it is relatively easy to cause immune rejection and lead to the risk of postoperative infection [138]. Therefore, in future studies before the use of allograft biomaterials, it is necessary to remove the immunogenicity and retain the complete three-dimensional structure and extracellular matrix components, so as to reduce the immune rejection after implantation into the host body.

4.5. Naturally derived biomaterials for rotator cuff repair

Naturally derived biomaterials are the most widely studied in the field of rotator cuff regeneration (39 studies were included). Collagen and decellularized matrix materials were the main subjects (a total of 21 studies). Compared with simple suture, most of the studies showed that naturally derived biomaterials produced better effect in promoting collagen fiber formation and healing at the tendon-bone interface. The meta-analysis showed that the maximum failure load and stiffness of naturally derived biomaterials were better than those of the simple suture group (rabbit model). One study [40] showed that collagen scaffolds had a negative effect on the strength in late healing period. It could be due to the fact that compared with normal tendons in rats (3.06 ± 0.6 mm), the patch used in the experiment (5-mm diameter, 1.8-mm thickness) was relatively large and thick, and it may be involved with the same thread of the fixation in the operation. The thread kept the bone, the patch and the rotator cuff together at the same time, and after the patch was absorbed locally, the tissue in the tie ring became smaller. This may cause the rotator cuff to loosen its contact with the bone, impeding tendon-bone healing. Large scaffolds may cause mechanical impact and external pressure on the healed tendons. Chung, S. W [68] showed that compared with simple tendon-bone suture, using patch did not improve tissue repair and biomechanical properties, which may be related to the surgical method and short follow-up time. In addition, at present, due to the advantages including broader source, low cost, and simple preparation technology, naturally derived biomaterials have become an important direction of tissue engineering research, but there may be some risks in the source of the materials, such as the pollution of bacteria, viruses and immune rejection [139], directly affecting the safety and effectiveness of this kind of materials. Therefore, how to reduce the residual antigens in naturally derived biomaterials and extend the evaluation time will be the focus of future research.

4.6. Patches loaded with growth factors or cells for rotator cuff repair

In recent years, different growth factors, such as platelet-derived growth factor-BB (PDGF-BB) [91,105], recombinant human PDGF-BB (rhPDGF-BB) [40,71], bFGF [32], FGF-2 [92], BMP-2 [116], BMP-7 [96], rhBMP-12 [84], rhBMP-2 [77,78], and TGF-β3 [83,106,118] were added to rotator cuff patches to enhance their effect on rotator cuff repair. The majority of experiments we included showed that patches added with factors were better than those without factors. However, two studies [83,116] showed that BMP-2 and TGF-β3 could not cooperate with the scaffold to promote tendon-bone healing. This may be due to inadequate dose of biological factors, strong scarring response of rodents, difference of factor species, but the specific mechanism is unclear. Growth factors have specific gene expression profile, which plays an important role in cell proliferation, differentiation, chemotaxis and synthesis of matrix. They can promote the increase of fibroblasts and collagen [140] and improve the orientation of collagen fiber [91] and biomechanical strength, which plays an important role in the induction of tendon-bone healing. Growth factors are essential to the regeneration of rotator cuff, which plays an irreplaceable role in the process of tissue repair. But so far the studies cannot fully explain the mechanism of action of growth factors in tendon-bone healing. In addition, the regulation function of growth factors is dose-dependent [40,71,92]. Therefore, how to choose the appropriate dosage of growth factors to achieve the best outcome and how to play a stable role in vivo due to the short half-life and easy degradation of growth factors [96,141] will be a highlight of future research.

Biomaterials loaded with cells can regulate the interaction between materials and cells, which plays an extremely important role in tissue repair. In the included studies, BMSCs [75,79,94,99,119,131], tendon-derived cells [142] and adipogenic stem cells [83] were loaded on the patches, and most studies showed that the group with cells loaded had better outcomes than the patch group without cells. Through the paracrine mechanism, BMSCs secrete cytokines/growth factors that play a positive role in the induction of cell proliferation and differentiation [143], and can also reduce inflammatory response by regulating macrophage [144]. But there are different sources of cells combined with the patches, what kind of cells having better synergy and the mechanism of interaction between cells and the patch material are still not clear. It is needed to further study the cell-material interaction and do the verification with more animal experiments in the future.

4.7. Experimental animal model and anatomical site of rotator cuff injuries

Current studies have shown that animal models of rotator cuff injuries are mostly rats, rabbits, sheep and dogs. The anatomical structure, pathogenesis, biomechanical properties, postoperative repair methods and follow-up time of these quadruped load-bearing animals are significantly different from those of humans. This is an important reason for the difference in outcomes between animal experiments and clinical trials of the materials for rotator cuff repair [96,105,109,112,120].

Although the animal models of rotator cuff injury have been relatively mature, and the rotator cuff injury sites mainly include supraspinatus tendon, infraspinatus tendon or supraspinatus and infraspinatus tendon which are both injured. No animal model can fully reflect the repair mechanism and physiological conditions of human rotator cuff injury, healing and regeneration [51]. Small animal models, such as rats and rabbits, are considered to be suitable models for studying the safety and performance of patch materials due to their advantages of low cost, easy management and large sample size. However, they have certain limitations in clinical translation [96,120]. For example, they are all small animals with small muscle volume, and operation is difficult to perform. Compared with humans, rats have stronger tendon-bone healing and regeneration ability. Moreover, rats rarely have obvious fatty infiltration after rotator cuff injury, and the

pathological process of chronic rotator cuff injury is quite different from that of humans [145], so human rotator cuff injury cannot be perfectly simulated. Compared with the rats, the rotator cuff injury in rabbits was bigger, and the results of autologous tissue and naturally derived biomaterials on the rotator cuff injury in rabbits were better. The healing process of large animals such as sheep and dogs is closer to the human, which are suitable model to study performance reliability and repeatability of surgical technique and biological mechanics [49,51]. The infraspinatus size and micro vascular system of sheep are similar to human, which is suitable model to study the pathological reaction process of rotator cuff injury, especially the change of chronic rotator cuff injury [71]. The advantage of the canine model is that the supraspinatus tendon can be repaired in a repetitive and accurate rehabilitation program. Therefore, large animal model is essential for the clinical translation of rotator cuff patch. In order to reduce the limitations of small animal models, future studies should use in vivo experiments in large animals to demonstrate sufficient clinical translational capacity. However, only 23.0% (17/74) of the studies in this review discussed the results of rotator cuff mesh materials in large animal models, and a relatively low proportion was insufficient to provide reliable data for clinical translation.

4.8. Sources of heterogeneity, internal authenticity and quality of evidence

This study strictly abided by the Cochrane intervention systematic review. We found that the current animal experimental evidence of the results for rotator cuff repair materials was of low quality, which reduced the reliability of the results and increased the risk of clinical translation, The main reasons are as follows.

Ideal repair materials in animal studies should have similar pathological mechanism to human beings [146]. In addition, low price of animal acquisition, easy feeding and management, low difficulty of surgical operation and relatively easy postoperative observation should also be considered. However, the studies included in this systematic review had great differences in animal species, rotator cuff injury model, repair materials, follow-up time and evaluation criteria. A total of 74 studies were included in this systematic review, involving five types of repair materials, four different animal models, three anatomical sites of rotator cuff injuries, three repair methods, and four types and degrees of rotator cuff injuries. For the follow-up time after rotator cuff repair, it was different for different animal models, and the evaluation criteria for the effect of histological repair were also diverse. In terms of histological outcomes, 36 studies were characterized qualitatively, and 38 had semi-quantitative scoring systems with inconsistent criteria (27 semi-quantitative scoring systems). For experimental research, quantitative analysis methods should be more scientific and rigorous [147]. The meta-analysis of homogenous quantitative data based on different studies can improve the inspection efficiency [148] and provide a scientific basis for subsequent experiments. Therefore, in future studies, appropriate animal models should be selected according to experimental purposes, and standardized surgical methods and consistent assessment and measurement methods should be established.

Randomization [149], allocation concealment [150] and blinding [151] are important measures to reduce the risk of internal bias in animal experiments. By controlling various risks of bias, it can effectively improve the internal authenticity of animal experiments. Most of the studies included in this systematic review had serious defects in experimental design, leading to high selectivity bias. Only 28 of the 74 studies were randomized controlled trials, of which 89.3% (25/28) did not report the method of randomized grouping, and 96.4% (27/28) did not report whether allocation concealment was implemented. The proportion of studies with unbalanced baseline characteristics was 64.9% (48/74). In addition, in the process of animal experiments, blind measurement of interventions and outcome evaluation, especially some subjective measures (such as histological indicators), is another important strategy to reduce the implementation bias and measurement bias, and to improve the authenticity and reliability of experimental results. However, none of the studies blinded the researchers or the feeders, and only 21.6% (16/74) of the studies blinded the evaluators. The sample size is an important factor in the selection of test statistics, which will affect the credibility of the results. In this study, only 14.9% (11/74) of the included studies provided the basis for the calculation of the sample size, and the mean of the included studies was 32, which accounted for more than 50% (58.1%) of the included studies. Therefore, These small sample studies significantly affected the baseline balance of the study. In addition, the unbiased report of experimental data is of great significance to the reliability of the conclusions of the systematic review. If the results of animal experiments are selectively reported, publication bias may occur and have a negative impact on the conclusions of the systematic review [152]. Although all the experimental results were described in detail in the method and results section of this study, there was no research proposal, so we could not judge whether the plan was strictly followed and whether there was selective report bias. Therefore, in future studies: 1) It is necessary to strictly design animal experiments based on the SYRCLE's standard, and report the whole process of the study in a detailed and comprehensive way according to the report specification in ARRIVE 2019 [153], so as to strictly control the quality of animal experiments and the transparency of the report; 2) It is necessary to refer to the clinical trial registration system established by WHO [154], encourage the registration of animal experiments, facilitate access to original data, to improve the transparency of the whole process of animal experimental research, and promote the clinical translation and utilization of its results [152,155].

4.9. Publication bias

In general, positive results are more likely to be published than negative results, and publication bias has implications for systematic review or health and social care relying on published literature as evidence [156]. It is necessary to encourage publication of negative results to reduce the impact of publication bias on results [157]. In this study, the maximum failure load (rat model) under biomechanical indicators was evaluated for publication bias, and the Funnel plot and Egger's test showed that there was no publication bias, indicating that the results were reliable.

4.10. Advantages and limitations

This systematic review is based on animal experiments to evaluate the effect of rotator cuff repair materials. It has the following strengths. This study was conducted in strict accordance with the production process of Cochrane intervention systematic review, and the risk of bias in animal experiments was assessed based on the internationally recognized SYRCLE's risk of bias assessment tool. Qualitative histological outcome indicators and quantitative biomechanical outcome indicators were evaluated according to GRADE-CERQual and GRADE tools, and the risk and feasibility of translating rotator cuff patches into clinical trials in animal models of rotator cuff injury were rigidly and scientifically evaluated. The limitation of this study is that there was no retrieval of conference abstracts and grey literatures, which may lead to the existence of publication bias. In addition, different rotator cuff injuries have different patch methods. After pre-subgroup analysis according to patch enhancement, bridging or interposition, the results are less robust due to the small number of included studies, so the number of studies should be increased for different surgical methods in the future to make the results more reliable.

4.11. Prospective

In recent years, due to the development of tissue engineering and regenerative medicine, rotator cuff patch is used as a repair method,

which is a new technology with rapid development and unlimited potential. Based on the comprehensive analysis of the basic information, methodological quality and evidence quality of the included studies, we found that the most common type of patch materials for rotator cuff repair was naturally derived biomaterials from a wide range of sources, autograft had the best outcome, and the most commonly used animal model was rat, but the rabbit model had better repairing results. However there are still some limitations in the current study. Future research should be continuous improvement in the following aspects: 1) To develop patches with safe and strong mechanical properties, easy source, easy storage and low cost, and with the appropriate dose of biological factors, cells, or with modification on the patch coating to achieve the best effect of rotator cuff mesh; 2) To explore animal models of rotator cuff injuries that can predict the clinical indications and reflect the function of rotator cuff repair materials according to the research objectives; 3) To standardize the subjective evaluation criteria for histological result, focus on the quantitative evaluation of outcome indicators, improve the authenticity and reliability of the study, and promote clinical translation; 4) To carry out the design and experimental scheme in strict accordance with random allocation, blind method and allocation concealment, and report the evaluation criteria and specific evaluation process in detail in the experimentation and quality control. In addition, it is suggested that the original research data of animal studies should be provided as an appendix online to improve the transparency of animal experiments, reduce the sources of bias, and promote the translation and application of research results.

5. Conclusions

In animal models, rotator cuff patches have some positive effect on rotator cuff repair, which can better promote the formation of collagen fibers at the tendon-bone interface and improve the biomechanical properties. At present, naturally derived biomaterials are most widely used rotator cuff patches, and autografts have the best effecacy in all the animal models, and rat is most common for animal model. Although the rotator cuff injury of rabbit model is greater than that of rat model, the rabbit model has better outcomes. Considering the current studies included have some limitations in terms of the inconsistency in experimental design and measurement standards, leading to the inconsistency in the conclusions of the studies, it is necessary to further improve experimental design, standardize animal model, ensure the consistency of evaluation standards, and provide more reliable laboratory evidence for clinical translation.

Funding

The article was supported by the Natural Science Foundation of China (Number: 81873184) and the National Innovation and Entrepreneurship Training Program for Undergraduate (No.202110730235).

CRediT authorship contribution statement

Jinwei Yang: Conceptualization, Methodology, Writing – review & editing. **Yuhao Kang:** Methodology, Software, Validation, Data curation. **Wanlu Zhao:** Writing – original draft. **Jia Jiang:** Conceptualization, Writing – review & editing. **Yanbiao Jiang:** Investigation, Writing – review & editing. **Bing Zhao:** Writing – original draft. **Mingyue Jiao:** Writing – original draft. **Bo Yuan:** Conceptualization, Writing – review & editing. **Jinzhong Zhao:** Conceptualization, Writing – review & editing. **Bin Ma:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioactmat.2021.08.016.

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