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Comparing Complications of Biologic and Synthetic Mesh in Breast Reconstruction: A Systematic Review and Network Meta-Analysis

Young-Soo Choi, MD[1] Hi-Jin You, MD, PhD[1] Tae-Yul Lee, MD, PhD[1] Deok-Woo Kim, MD, PhD[1]

[1] Department of Plastic and Reconstructive Surgery, Korea University Ansan Hospital, Ansan, Republic of Korea

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Address for correspondence Tae-Yul Lee, MD, PhD, Department of Plastic and Reconstructive Surgery, Korea University Ansan Hospital, 123 Jeokgeum-ro, Danwon-gu, Ansan 15355, Republic of Korea (e-mail: tylee0919@hanmail.net).

Abstract

Background In breast reconstruction, synthetic meshes are frequently used to replace acellular dermal matrix (ADM), since ADM is expensive and often leads to complications. However, there is limited evidence that compares the types of substitutes. This study aimed to compare complications between materials via a network meta-analysis.

Methods We systematically reviewed studies reporting any type of complication from 2010 to 2021. The primary outcomes were the proportion of infection, seroma, major complications, or contracture. We classified the intervention into four categories: ADM, absorbable mesh, nonabsorbable mesh, and nothing used. We then performed a network meta-analysis between these categories and estimated the odds ratio with random-effect models.

Results Of 603 searched studies through the PubMed, MEDLINE, and Embase databases, following their review by two independent reviewers, 61 studies were included for full-text reading, of which 17 studies were finally included. There was a low risk of bias in the included studies, but only an indirect comparison between absorbable and non-absorbable mesh was possible. Infection was more frequent in ADM but not in the two synthetic mesh groups, namely the absorbable or nonabsorbable types, compared with the nonmesh group. The proportion of seroma in the synthetic mesh group was lower (odds ratio was 0.2 for the absorbable and 0.1 for the nonabsorbable mesh group) than in the ADM group. Proportions of major complications and contractures did not significantly differ between groups.

Conclusion Compared with ADM, synthetic meshes have low infection and seroma rates. However, more studies concerning aesthetic outcomes and direct comparisons are needed.

Keywords
- mammaplasty
- surgical mesh
- network meta-analysis

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Introduction

The average 5-year survival rate for women with nonmetastatic breast cancer is 90%, and the average 10-year survival rate is 84%, which is high compared with other invasive cancers.[1] Accordingly, not only survival rates but the results of breast cancer surgery as an indicator of a great evaluation of life following breast cancer surgery are receiving considerable attention. Although cancer is invisible to the patient, the results of reconstructive plastic surgery immediately after breast cancer surgery can be significant because the condition after surgery for cancer treatment can be assessed by oneself. Therefore, the importance of immediate breast reconstruction, which has been markedly developed since 2005 for supporting muscles by meshes, has increased, and the types of mesh and surgical techniques have been developed in various ways.[2]

Meshes for breast reconstruction are divided into two major categories. The first, biological mesh, is called acellular dermal matrix (ADM) and is formed using cells of animals such as bovines. The second classification, synthetic mesh, is divided again into an absorbable type (such as Vicryl, TIGR, or Phasix) and a nonabsorbable type (such as Breform or TiLoop) according to the absorbency of the mesh; here, numerous products have been developed and are being used variously without having been evaluated thus far.[3]

If there are such a variety of options, it may be difficult to determine the mesh type, and whether to use the mesh should be determined when the surgeon first performs breast reconstruction. There may be more interest in the probability of complications such as infection or contracture after surgery. However, there is limited evidence of superior options regarding the results of breast reconstruction. Although an animal study reported a lower capsular contracture rate in biologic mesh than in the synthetic type, only one randomized controlled human study demonstrated more giant cells and foreign body reactions in synthetic meshes but no difference in capsular contracture.[4] Furthermore, most studies compared two substitutes or nonmesh patients, which do not help the selection of mesh.[5] Therefore, it might be helpful to surgeons and patients to compare all meshes in one standard with complicated meta-analysis methods. Focusing on this part, we conducted a systematic review by collecting research conducted thus far and performing a network meta-analysis about complication rates of meshes by various mesh types. All reported participants who received one-step breast reconstruction surgery in the past 10 years were included for this review, and the mesh types used during surgery were collected for the classification of interventions. After screening the eligible studies, we classified adverse events of selected studies and conducted a meta-analysis. The network meta-analysis method was used in this study, which can compare various interventions in a single analysis either directly or indirectly. Through this method, we could compare the adverse effect rates of each mesh type, even if no studies directly compare interventions with one another.

Methods

We followed the extension statement for the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) incorporating network meta-analyses guidelines, which are specific guidelines to be followed when conducting a network meta-analysis.[6] We systematically reviewed observational and randomized controlled trials on humans reporting any type of complications with breast reconstruction cases from 2010 to 2021 in the PubMed, MEDLINE, and Embase databases. Nonhuman studies, conference abstracts, non-English articles, single-arm studies, and studies not including outcomes within 3 months after surgery were excluded from the systematic review. Two-stage surgeries were also excluded for comparability. We selected single-stage surgeries, including breast reconstruction with any type of mesh, which reported complications at 6 or more months after surgery as an intervention. Complications due to breast reconstruction were defined as any medical conditions requiring treatment following the surgery, including both systematical and local events. The keywords included the specific person (breast reconstruction OR mastectomy OR mammaplasty), intervention (synonyms or product names of biological or synthetic mesh), AND outcomes (adverse event OR complication). The search was performed on August 31, 2021. Two independent authors screened for the eligible studies, and all authors agreed to select the final studies included in the meta-analysis.

After screening the reported complications of breast reconstructions, we classified the interventions (materials of mesh) into the following four categories: ADM (biologic mesh), absorbable synthetic mesh (Vicryl, TIGR, or Phasix), nonabsorbable synthetic mesh (Breform, TiLoop, or Seragyn), and no mesh used. Partially resorbable synthetic meshes such as Seragyn were included in the nonabsorbable category. Biological meshes included compositions from porcine or bovine. However, DualMesh, a nonabsorbable synthetic mesh, was excluded from the analysis, since the research reporting the complication rate of this substitute demonstrated a high risk of bias for inclusion in the meta-analysis.[7]

The main outcome was classified as the proportion of infection, seroma, major complication, or contracture following breast reconstruction. Infection and seroma were included since they are commonly described complications in breast reconstruction studies. Infection included any type of inflammation on the surgical side within 3 months. The reported seroma formation of the reconstructed site was collected and summarized as the proportion. Capsular contracture and major complications were also included as outcomes, since they might be important when surgeons select the mesh type. All classes of capsular contracture were considered to be the complication named contracture.[8] Major complications included all cases of reoperation or removal of the implant.[9]

We performed a network meta-analysis of the four categories of interventions. A network was constructed as the parallel radials with no direction, allowing for

Table 1 Summary of included breast reconstruction studies comparing complications by mesh type

No	Author, year	Case numbers	Intervention[a]	Outcomes[b]
1	2021, Sewart et al[2]	95/174/495	A/C/D	Infection (I) / major complication (MC)
2	2021, Schüler et al[24]	54/94/40	A/C	I / Seroma (S) / MC
3	2021, Hansson et al[19]	24/24	A/B	I / S / MC
4	2020, Hansson et al[20]	24/24	A/B	S / MC
5	2020, Gao et al[16]	79/76	A/D	I / S / capsular contracture (CC) / MC
6	2019, Potter et al[23]	236/436/1121	A/C/D	I / MC
7	2019, Hallberg et al[18]	49/72	A/B	CC / MC
8	2019, Eichler et al[3]	192/128	A/C	I / S / MC
9	2019, Chen et al[12]	32/27	C/D	I / S / CC / MC
10	2016, Gschwantler-Kaulich et al[17]	25/23	A/C	I / S / MC
11	2016, Baldelli et al[9]	70/136	C/D	I / S / CC / MC
12	2015, Ganz et al[5]	112/46	B/D	I / S / CC / MC
13	2015, Dieterich et al[15]	42/48	C/D	I / S / CC / MC
14	2014, Colwell et al[14]	201/31	A/B	I / S / MC
15	2012, Hill et al[21]	36/43	A/D	I
16	2011, Liu et al[22]	266/204	A/D	I / MC
17	2010, Chun et al[13]	269/146	A/D	I / S

[a]Intervention is categorized as follows: A: ADM (biologic mesh); B: absorbable synthetic mesh (Vicryl, TIGR, or Phasix); C: nonabsorbable synthetic mesh (Breform, TiLoop, or Seragyn); and D: no mesh used.
[b]Only used complications in this study are described.

comparison between any two meshes. Since the studies comparing two categories of synthetic meshes are missing, only indirect odds were evaluated between the two mesh types, which could lead to potential bias, such as reporting bias. Therefore, direct evidence proportions were also reported as the result. The odds ratio and 95% confidence intervals (CI) were estimated. All models used random effect models, considering the differences between included studies and within groups, since all studies showed heterogeneous study concepts and designs. We used the "netmeta" package of the R program for a network formation and frequentist network meta-analysis. Direct evidence plots were estimated to present the proportions of direct comparisons between groups. Risks of bias were evaluated by the guideline of the Risk Of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool, since it can cover the evaluation of observational studies.[10] According to the ROBINS-I tool, risks of confounding, selection bias, information bias, and reporting bias were evaluated by two independent reviewers and reported as three levels: low, moderate, or high risk of bias. To check the inconsistency between direct and indirect comparisons in the multiarm network structure, we performed the global and local approach of Cochrane's Q test and decompressed the design using the "netsplit" function of the "netmeta" package in R. *p*-Values are considered to be significant if they are less than 0.05, and all statistical analyses and graphics were created by R 3.4.0.[11] Last, we performed sensitivity analysis while excluding studies serially to avoid any reporting bias to control the heterogeneity.

Results

Of 603 searched studies through the PubMed, MEDLINE, and Embase databases, following their review by two independent reviewers, 61 studies were included for the full-text reading, of which 17 studies were finally included for the network meta-analysis.[2,3,5,9,12–24] Only two studies[19,20] had the same author among the controlled studies, as the remaining studies were retrospective cohort studies. The author, published year, case numbers, types of intervention, and outcomes are summarized in ►**Table 1**. In the early 2010s, ADM materials were frequently compared with no use of mesh methods. However, since 2016, various mesh substitutes were compared with one another through their complications, such as infection, seroma, capsular contracture, or major complications (reoperation or explantation).

The final network graphs of each outcome are illustrated in ►**Fig. 1**. The network was constructed based on the proportion of case numbers of interventions, which was evaluated as the sum of case numbers of the intervention in the included studies and had no directions to the specific intervention. No direct comparison was made between absorbable and nonabsorbable synthetic mesh; therefore, only an indirect comparison between two synthetic substitutes was possible. Other substitutes were compared in various connections, which exhibited different proportions (indicated as the thickness of the line) by the type of complication.

Complication rates of each intervention were compared, and their odds ratios are described in ►**Fig. 2**. In aspects of

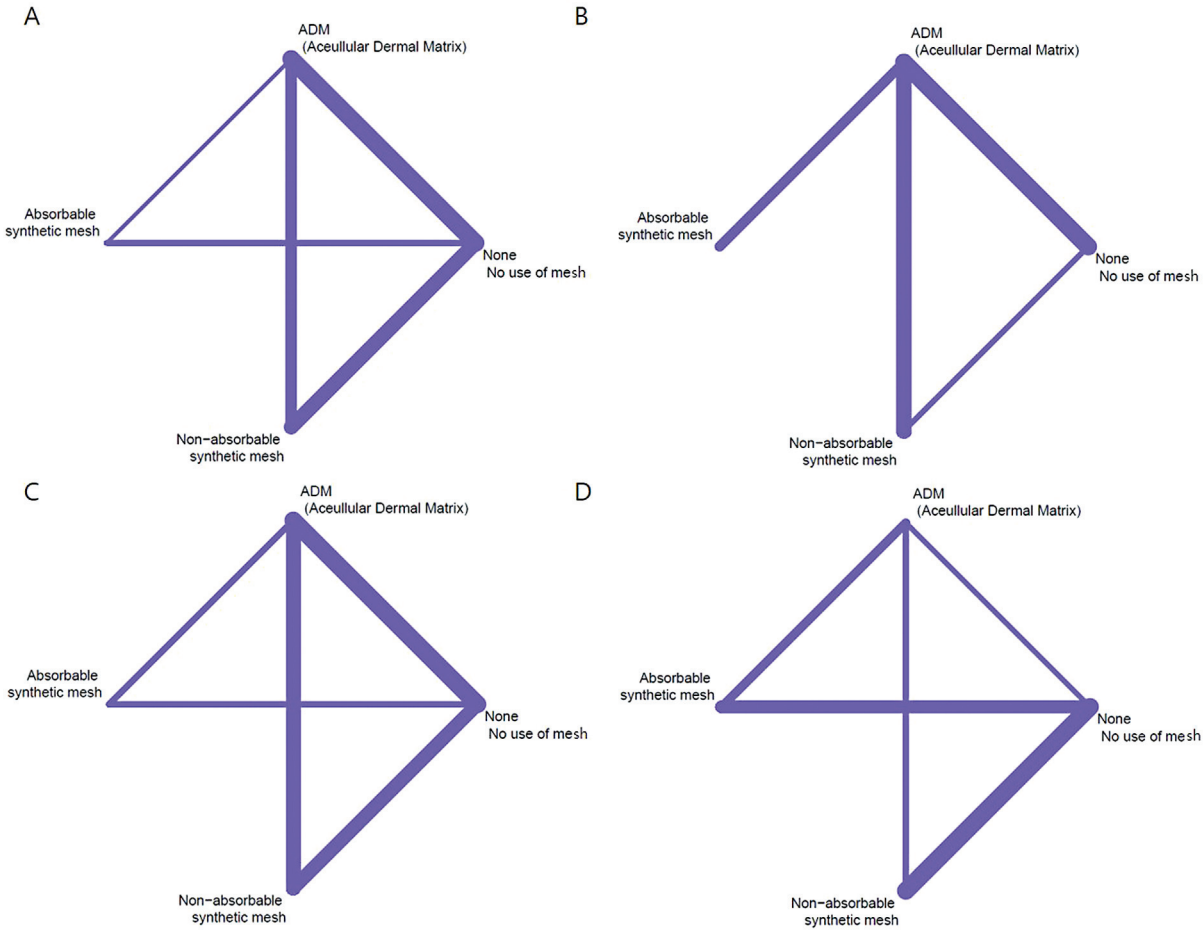

Fig. 1 Network graphs of each outcome. (**A**) Infection, (**B**) seroma, (**C**) major complications, and (**D**) capsular contracture.

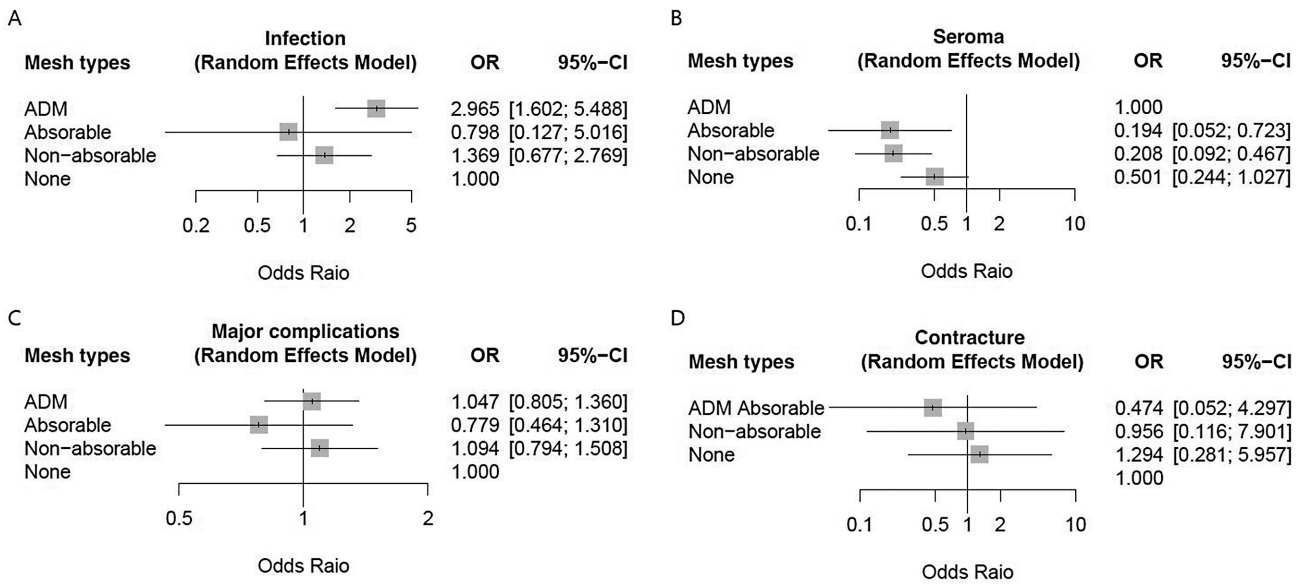

Fig. 2 Forest graphs of the odds ratio (OR) of complication rates between groups. (**A**) Infection, (**B**) seroma, (**C**) major complications, and (**D**) contracture. ADM, acellular dermal matrix; CI, confidence interval.

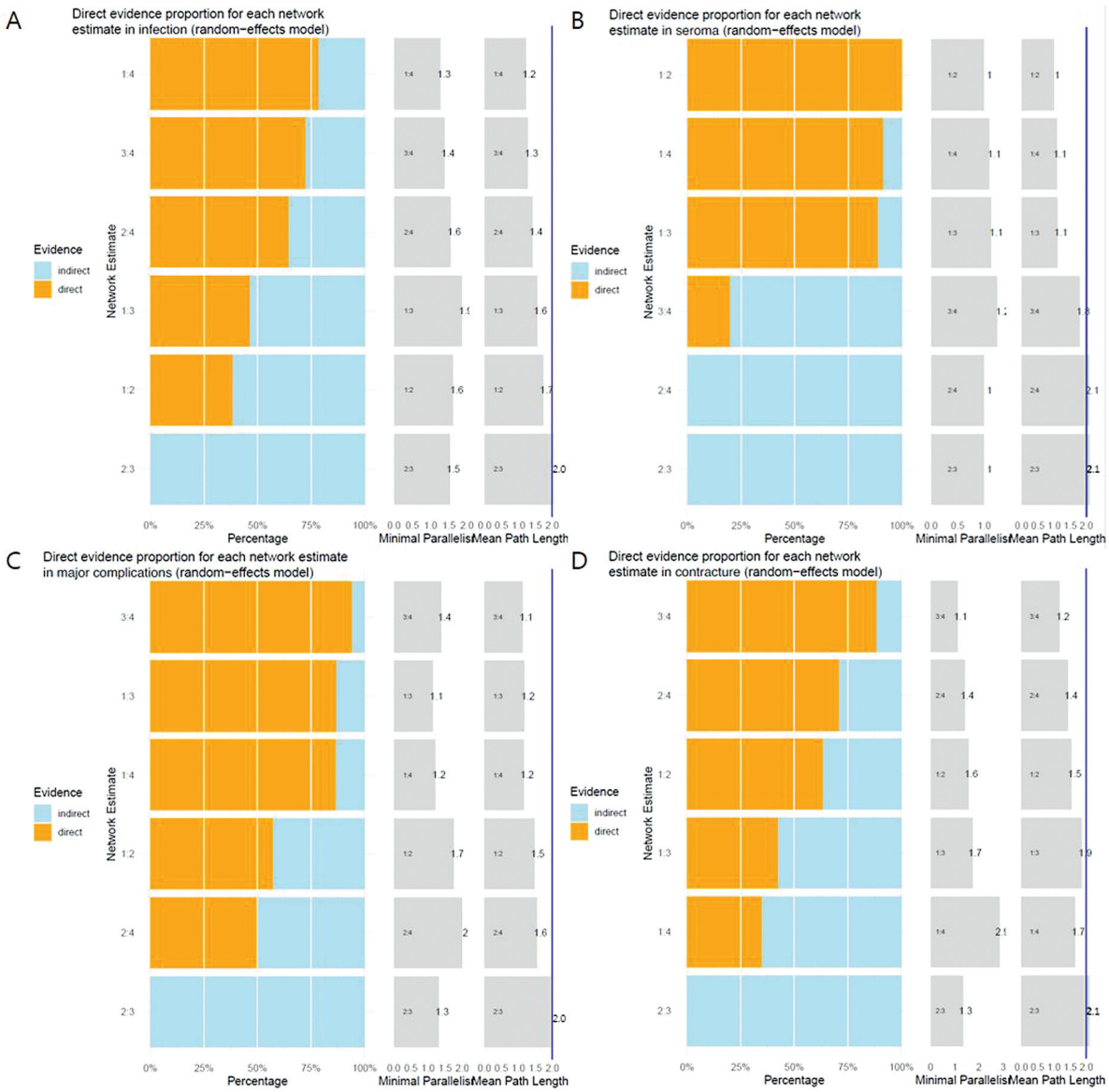

Fig. 3 Direct evidence proportions for each network between groups. Evidence plots 1 to 4 indicate the acellular dermal matrix, absorbable synthetic mesh, nonabsorbable synthetic mesh, and nomesh groups in order. (**A**) Infection, (**B**) seroma, (**C**) major complication, and (**D**) contracture.

infection, there was a 2.97 (95% CI: 1.60–5.49) times higher infection rate in the ADM group than in the nonmesh group (►**Fig. 2A**). However, two synthetic mesh groups exhibited no significant difference with the nonmesh group in terms of infection rate (►**Fig. 2A**).

In the aspect of seroma, the proportion of seroma in the synthetic mesh group was significantly lower (odds ratio = 0.19 for absorbable synthetic groups and 0.21 for the nonabsorbable synthetic group) than in the ADM group (►**Fig. 2B**). However, the ADM group and nonmesh group demonstrated no significant difference in the seroma formation proportion.

The major complication rate and contracture rate did not differ by group. The absorbable synthetic mesh group demonstrated a lower tendency of major complication rates, but it was not statistically significant. The nonabsorbable synthetic mesh group showed a similar distribution compared with the ADM group. Moreover, the capsular contracture rate was heterogenous within the groups, leading to a nondifference between them.

Direct evidence proportions for each network estimate are presented in ►**Fig. 3**. In all outcomes, direct comparison between two synthetic meshes was difficult. Additionally, the proportion of indirect comparison was higher than other pairs in the synthetic mesh groups and nonmesh group, especially when comparing the seroma formation. To address inconsistency, Cochrane's Q test and decompression methods are used through four outcomes. In the global approach, between or within designs did not exhibit significancy in four outcomes (p-value > 0.05). Furthermore, in the local approach, there was no significant difference between the direct and indirect method in all categories (p-value > 0.05), indicating less of a problem with network construction in this study.

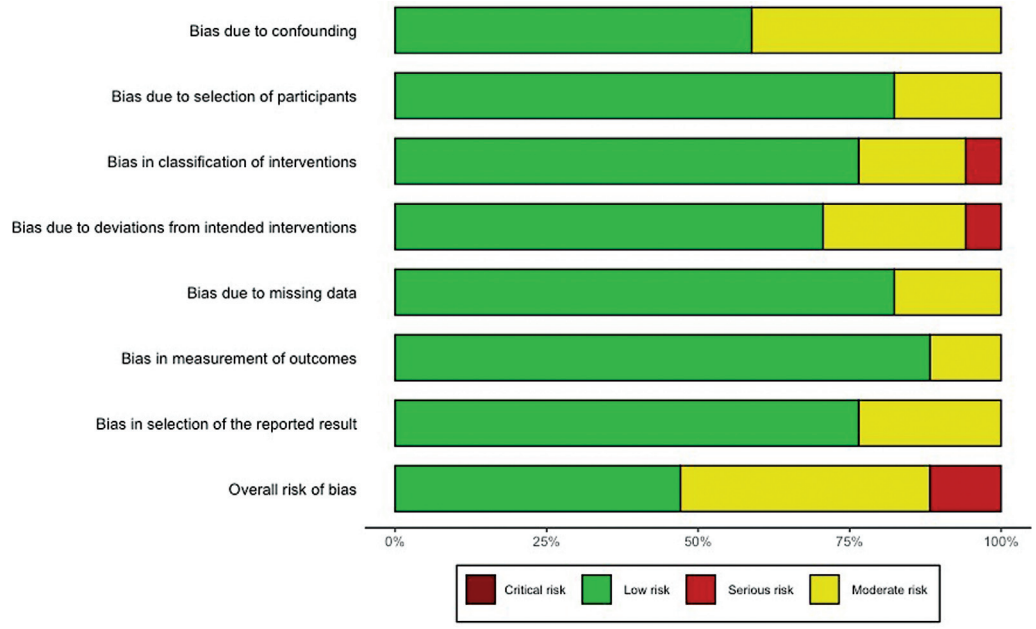

Fig. 4 Summarized estimated risk of bias among included studies.

According to the ROBINS-I risk-of-bias assessment guideline, seldom was there a moderate or serious risk of bias in some domains in terms of the classification of interventions or intended interventions, since some studies used only nonrandomized observational studies for the comparison (►**Fig. 4**). However, most studies exhibited a low risk of bias in the five other domains, and there were no critical risks of bias assessed by the researchers.

Discussion

Compared with the use of ADMs or no use of meshes, synthetic meshes tend to have low infection and seroma rates. This result was significant in absorbable synthetic meshes, which are widely used these days as substitutes for ADMs. Since the technique for immediate breast reconstruction is developing rapidly, many substitutes were applied as a mesh for muscle and tissue fixation during surgery.[25] However, there is no single standard of the use of meshes, leading to heterogenous choices by surgeons.[2] This heterogeneity cannot only lead to unexpected adverse effects, such as infection or explantation, but also make it difficult to compare the result of reconstruction after surgery. Therefore, it is crucial to systematically review and categorize the reported complications of meshes. Since this study was constructed and organized simultaneously by writers, it unfortunately is not registered in any preregistration program. Moreover, results for each included study were difficult to describe separately, since some studies were not intended to report complication rates on purpose but were just calculated by reviewers.

There are other limitations in this study as well. First, no direct comparison was made between synthetic meshes, namely the absorbable and nonabsorbable types, since no two-arm study reported their relationship. Therefore, only indirect comparison was possible within these two categories. However, we used the random effects model to consider the heterogeneity both between and within studies. Additionally, a network meta-analysis was performed, and a rank test for each category was evaluated separately by groups. Still, more studies concerning aesthetic outcomes and direct comparisons are needed. Second, since the retrospective studies are included in the meta-analysis, it was difficult to control the surgery indication or method in selecting the studies. Instead, the evaluation method or the definition of outcomes (complications) is strictly controlled when selecting the final studies for meta-analysis. Outcomes to compare were limited to four categories, since the settings and definition of complications were heterogenous by study. A unified standard evaluating the adverse effects is needed to assess the cosmetic results with breast-Q for further systematic reviews. Through the standardization, other complications such as hematoma and implant loss might be able to be compared between groups. Last, two-staged reconstructions were excluded from the meta-analysis, since it was difficult to synthesize the follow-up times, terms between surgeries, and timing of complications. Nevertheless, to our knowledge, this is the first meta-analysis to apply network meta-analysis methods to compare between four categories using primarily two-arm studies. Moreover, we evaluated various aspects of adverse effects when using meshes in breast reconstruction, which indicated no elevated risks in the synthetic mesh groups.

In this study, compared with ADMs, synthetic meshes had low infection and seroma rates. Therefore, they may be an appropriate substitute for breast reconstruction. Especially, absorbable synthetic meshes demonstrated more homogenous safe results than nonabsorbable synthetic meshes. The reason for the low risk of infection or seroma is not clear, but one study reported lower bacteria-mediated biofilm

formation than ADMs in vitro.[26] Considering the low cost and satisfactory surgery results in retrospective and animal studies,[25] absorbable synthetic meshes might be considered the gold standard method for the immediate breast reconstruction technique.

Authors' Contributions

Y.S.C. and T.Y.L. conceptualized the study. Y.S.C. and H.J.Y. contributed to data curation and formal analysis. Y.S.C. and D.W.K. contributed to methodology, project administration, and visualization. YS Choi helped in writing—original draft. Y.S.C. and T.Y.L. contributed to writing—review and editing.

Conflict of Interest

D.W.K. is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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