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Breast

Comparing the Outcome of Different Biologically Derived Acellular Dermal Matrices in Implant-based Immediate Breast Reconstruction: A Meta-analysis of the Literatures

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Background: Acellular dermal matrices (ADMs) have been used extensively in implant-based breast reconstruction. It was reported that due to the different sources and processing methods, the outcomes of ADMs in implant-based breast reconstructions are expected to differ. We designed this study to statistically analyze and discuss the outcome of 3 commonly used ADMs, Alloderm, Strattice, and Surgimend in implant-based breast reconstruction.

Methods: Comprehensive review of the literatures searched on electronic databases was done to identify studies published between 2006 and 2017 comparing the outcome of ADMs. Pooled random effect estimates for each complication and 95% confidence interval (CI) were calculated. One-way analysis of variance and Bonferroni test were used to compare statistical significance between and within groups, respectively. Multiple linear regression was done to include confounding factors and R statistic program for forest plot.

Results: Twenty-one studies met the inclusion with a total of 1,659, 999, and 912 breasts reconstructions in Alloderm, Strattice, and Surgimend, respectively. Seven complications extracted including major and minor infection, seroma, implant loss, hematoma, capsular contracture, and localized erythema. Pooled total complication rates were 23.82% (95% CI, 21.18–26.47%) in Strattice, 17.98% (95% CI, 15.49–20.47%) in Surgimend, 16.21% (95% CI, 14.44–17.99%) in Alloderm. Seroma rate was the highest in Strattice group (8.61%; 95% CI, 6.87–10.35%). There was no statistical significance between and within groups.

Conclusion: Although Strattice exhibited a higher overall pooled complication rate compared with Alloderm and Surgimend, the incidence of individual complication varies between studies. A cost analysis of different ADMs may aid in choosing the type of ADMs to be used. (*Plast Reconstr Surg Glob Open 2018;6:e1701; doi: 10.1097/GOX.0000000000001701; Published online 19 March 2018.*)

INTRODUCTION

Acellular dermal matrices (ADMs) are biomaterials used extensively in the last decade in implant-based breast reconstructions with successful outcomes and acceptable complication rates.[1,2] The approach of using this technique is attributable to the ability to perform skin-sparing or nipple-sparing mastectomies.[3] First introduced in 2001, Salzberg et al.[3,4] has successfully introduced its use to provide implant coverage at the inferolateral pole of the breast in implant-based breast reconstructions.

It was reported that due to the different source and processing methods, the outcomes in the use in implant-based breast reconstruction are expected to differ.[4] In this study, we will be discussing and analyzing 3 of the most commonly used ADMs in implant-based breast reconstructions, which are Alloderm (LifeCell Corp., Branchburg, N.J.), Strattice (LifeCell Corp., Branchburg, N.J.), and Surgimend PRS (TEI, Biosciences, Inc., Boston, Mass.).

AlloDerm, the most commonly and widely investigated ADM, is a human-derived ADM commonly used in the

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United States and has not received the European Conformity (CE) marking for licensed used in Europe.[5] Alloderm is an ADM with reduced antigenicity that is produced from the epidermis human cadaveric skin. Alloderm was described as an ADM that is able to incorporate with host tissue via new matrix formed from specialized stem cells, which allowed for tissue regeneration.[6] Up until 2013, Alloderm, then known as Regenerative Tissue Matrix, was not terminally sterilized[6] contrary to Strattice and Surgimend. The Ready-to-Use counterpart was terminally sterilized.

Strattice is a noncrosslinked porcine-derived xenogeneic ADM. It is derived from porcine fetal dermis.[5,7] It became available at the end of 2008 and was licensed to use in Europe. Due to the limited availability in human cadaveric skin, Strattice has its advantages.[7] The structure and collagen arrangement of Strattice is almost similar to human cadaveric ADMs. It has undergone processing to maintain the integrity of the extracellular matrix allowing Strattice to act as a scaffold for cellular regeneration and neovascularization with hopes of reduced xenogeneic rejection response.[5,8]

SurgiMend, similar to Strattice, is a xenogeneic, noncrosslinked ADM, which is a fetal bovine-derived dermal collagen.[9,10] Studies have shown that it is rich in collagen types I and II[5] and described by manufacturers and study stating that it is rich is collagen type III.[6,11] These may facilitate tissue regeneration by impeding scarring.

Manufacturing

The manufacturing steps behind an ADM largely govern its subsequent functional properties in situ. One ADM can vary from another by either its source and/or processing of the tissue. Independent of the source, the tissue undergoes a decellularization process in which the extracellular matrix is isolated. The method of isolation varies between different types of ADMs but can be largely categorized into mechanical and more commonly chemical or biological processing.

The primary purpose of decellularization is to reduce the immunogenicity of the scaffold material so that it is host-compatible. In general, decellularization helps to augment the reconstructive capabilities of surrounding tissues.[12,13] The commonest methods of decellularization are chemical and biological including the use of trypsin/triton,[14] sodium hydroxide (NaOH),[15] sodium dodecyl sulfate, and sodium deoxycholate.

Following decellularization, the dermal scaffolds then undergo terminal sterilization process by various methods including ultraviolet radiation, gamma radiation, and supercritical fluid techniques including use of CO_2.[16,17] Before shipment, the matrix is stored in a hydrated form or lyophilized to dry; then rehydrated for usage.[18]

METHODS

We have conducted a meticulous literature search on the databases Embase, Pubmed, and Medline, looking at literatures published from 2006 to 2017 in all 3 databases on the use of ADMs in implant-based immediate breast reconstruction. Search terms that were used include acellular dermal matrix, Acellular dermal matrices, ADMs, Breast reconstruction, breast implantation, breast implants, strattice, surgimend, alloderm, porcine, bovine, human ADM, complications, outcome, properties, collagen, seroma, infections, capsular contracture, hematoma, implant loss, explantation localized inflammation, localized erythema, and red breast syndrome.

Data Extraction

Primary outcome of interest for this meta-analysis was incidence of postoperative complications. Seven common complications associated with the use of ADMs in implant-based breast reconstruction were identified in the literatures, which were major infections classified as infections including cellulitis that were required readmission to theatre, minor infections classified as infections that were treated with oral or intravenous antibiotics that resolved without further complications, seroma, hematoma, implant loss, localized inflammation. Localized inflammation is erythema of the overlying skin in the absence of cellulitis or erysipelas or other skin infections and was not classified under complications in most studies. Figure 1 showed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart for the selection of articles.

The group of authors have also listed a series of inclusive criteria for the study, including all original studies on alloplastic/implant-based breast reconstruction with the use of ADMs, different biologically derived ADMs used in breast reconstruction, Alloderm, Strattice, and Surgimend. Additional data that were extracted were first authors; study institution; publication year; follow-up (mean/median); types of ADMs used, Alloderm, Strattice, and Surgimend; data for procedural characteristics; patient's body mass index (BMI); confounding risk factors such as smoking, diabetes, neoadjuvant and adjuvant chemotherapy, and radiotherapy.

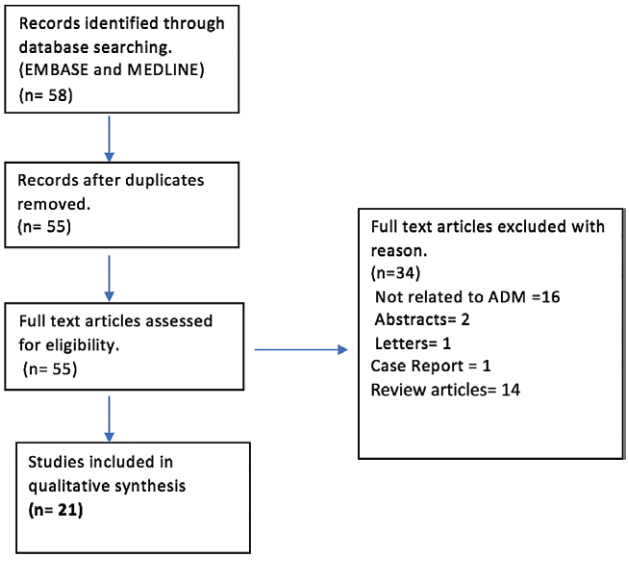

Fig. 1. Study attrition diagram.

Exclusion criteria were review articles, discussions, published abstracts, case reports, articles written in non-English language, and articles published before 2006.

Statistical Analysis

Pooled random effect estimates for each postoperative complication and 95% confidence interval (95% CI) were calculated using Microsoft Excel. Using IBM SPSS Statistics for Windows (Version 22.0. Armonk, NY: IBM Corp.), one-way analysis of variance (ANOVA) and Bonferroni test were used to compare statistical significance between and within 3 groups, respectively. Multiple linear regression was done to include confounding factors. Using the complication rate and 95% CI, findings were presented on a forest plot using R Statistics (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.).

Risk of Bias Assessment

Cochrane risk of bias tool was used for risk bias assessment (Table 1). Studies were assessed for performance outcome bias, selective reporting bias, attrition bias, and funding bias. Low, fair, and high outcome levels were ranked in each study based on the level of biasness.

RESULTS

A total of 58 publications were identified in the initial search on PubMed, Ovid, Medline, and Embase. Using predefined exclusion and inclusion selection criteria, 2 literatures were found to be duplicate, 16 literatures were not related to ADMs, 3 abstracts, 1 letter, 1 case report, and 14 reviews were excluded resulting in 21[1–5,7–11,19–29] studies that were eligible for this meta-analysis. Four of these studies were comparative studies of ADMs; therefore, we have stratified these data as individual studies[5,9,10,19] making a total of 25 studies. All of these studies satisfied criteria for the study of ADMs used in implant-based immediate breast reconstruction.

Eight Alloderm studies, 11 Strattice studies, and 6 Surgimend studies were identified for our analysis. As described in Table 1, in the studies that were assessed using Cochrane Risk of Bias Tool, 12 studies had high risk, 5 studies had low risk, and 4 studies had fair risk of bias.

Patient demographics, risk factors, and indication for surgery were pooled together in Table 2. The total number of implant-based immediate breast reconstructions were 1,659 breasts, 999 breasts, and 912 breasts involving the use of Alloderm, Strattice, and Surgimend, respectively. Majority of the cases were indicated for invasive mastectomies, followed by prophylactic mastectomies with only a total of 1 revision and 7 delayed mastectomies as reflected in Table 2.

From the literatures that were investigated, the patients age range were 31.9–58.5 years. Only 6 studies reported the mean mastectomy weight and axillary node clearance surgery. All of the studies reported patients who had adjuvant chemotherapy and radiotherapy. Patient's comorbidities, history of chemotherapy, radiotherapy, and axillary node clearance surgery may affect postsurgical outcomes, and this will be discussed further in discussion.

Six common complications associated with the use of ADMs in implant-based breast reconstruction were identified in the literatures. Pooled complication rates are listed in Table 3. This showed a higher overall complication rate (23.82%) in the Strattice group as compared with Surgimend (17.98%) and Alloderm (16.21%), which had the best overall outcome. Incidence of individual complications of each group were listed in Tables 5–7. The most common complication was major infections in Alloderm (3.80%; CI, 2.88–4.72%) and seroma in Surgimend (4.61%; CI, 3.24–5.97%) and Strattice (8.61%; CI, 6.87–10.35%). Strattice was also found to have the highest incidence of localized inflammation at 3.3% (95% CI, 2.2–4.41%) as seen in Table 8.

One-way analysis of variance test was computed on SPSS, and it was found that there were no significant statistical differences between all 3 groups. Bonferroni analysis was then done to compare the *P* value between groups, and there were no significant differences as depicted in Table 4. Further analysis of the outcome data by taking account for confounding factors, a multiple linear regression analysis was carried out. It was found that confounding factors did not significantly affect the outcome associated with the use of ADMs with the exception of minor infection rates in predictor group (d), which had a regression significance of $P = 0.034$ as seen in Table 9.

The occurrence of major infections was plotted in Figure 2, and it was statistically assumed that in 95% of these intervals intersection was at about 5.5%. Evgeniou et al.[22] had much smaller number of cases; hence a larger CI had a much deviated and higher complication rate (23.8%; 95% CI, 5.59–42.02%) associated with the use of Strattice. In Figure 3, minor infection rates were significantly higher in study by Lardi et al.[23] with the use of Strattice at 11.5% in 200 breasts (95% CI, 7.08–15.92%) and Liu et al.[24] at 8.5% in 165 breasts (95% CI, 4.23–12.73%). Salzberg et al.[3] reports a very small number of complication at 0.2% in 466 breast reconstructions (95% CI, -0.21% to 0.63%).

Seroma rate associated with the use of Strattice had the highest (8.61%) pooled complication. In Figure 4, Strattice studies, Dikmans et al.,[7] Hille-Betz et al.,[25] and Evgeniou et al.[22] reported a complication rate of 20.9%, 20.4%, and 19%, respectively. In Alloderm group, pooled complication rates were the lowest at 3.07%. Glasberg and Light,[19] Butterfield,[10] and Gdalevitch et al.[1] reported an individual seroma rate of 21.4%, 15.7%, and 10.4%, respectively. Surgimend group has a pooled seroma rate of 4.61%. A comparative study[10] reported a lower seroma rate at 8.5% (95% CI, 5.62–11.47%) in 351 cases compared with Alloderm, which had a rate of 15.7% (95% CI, 8.17–23.29%) in 89 cases.

Implant loss rate associated with the use of Strattice was the highest (5.61%) pooled complication. According to Figure 5, there was significantly higher implant loss rate in Strattice studies by Evgeniou et al.[22] Dikmans et al.,[7] and Lardi et al.[23] 23.8% (95% CI, 5.59–42.02%), 11.8% (95%

Table 1. Risk Bias Study of the Literatures

	Study Demographics					
References	**Study Design**	**Type of ADM**	**Comparator ADM**	**Sample Size**	**Follow-up Stated**	**Outcome Reported**
Salzberg et al.[3]	1. Retrospective cohort 2. Nonrandomized	Alloderm	Noncomparative	466 Breasts	28.9±21.3 mo	1. Total complication rate: 19 (4.1%) 2. Types and incidence of complications associated with the use of Alloderm in immediate breast reconstruction. 3. A comparison of complications in oncologic breasts and prophylactic breasts
Gdalevitch et al.[1]	1. Retrospective cohort 2. Nonrandomized	Alloderm	Noncomparative	164 Breasts	Median 228 d	1. Total complication of 96 (58.5%) 2. Types and incidence of complications associated with the use of Alloderm in immediate breast reconstruction 3. Predictors of failures statistical measurement
Ricci et al.[9]	1. Retrospective cohort 2. Nonrandomized	Alloderm	Surgimend	578 Breasts in Alloderm	Mean 587 d	1. Total complication rate in Alloderm 174 (30.1%) 2. Operative factors measured 3. Multivariate analysis done
				374 Breasts in Surgimend	Mean 587 d	1. Total complication rate in Surgimend 68 (18.2%) 2. Operative factors measured 3. Multivariate analysis done
Spear et al.[21]	1. Prospective cohort 2. Nonrandomized	Alloderm	Noncomparative	58 Breasts	25.9	1. Total complication rate of 8 (13.8%) 2. Mean intraoperative expander fill 3. Incidence of complication in irradiated and nonirradiated breast
Liu et al.[24]	1. Retrospective cohort 2. Nonrandomized	Alloderm	FlexHD	165 Breasts in Alloderm 97 Breasts in FlexHD	6.4	1. Total complication rate of 47.3% 2. Immediate versus delayed risk factors and complications 3. Complications in ADM versus no ADM 4. Multivariate analysis of complications
Gamboa-Bobadilla[28]	1. Retrospective cohort 2. Nonrandomized	Alloderm	Noncomparative	13 Breasts	14	1. Total complication rate of 3 (23.1%) 2. Complications related to the use of Alloderm 3. Histological analysis
Butterfield[10]	1. Retrospective cohort 2. Nonrandomized	Alloderm	Surgimend	89 Breasts in Alloderm 351 breasts in Surgimend	32.8±15.87 15.6±8.79	1. Total complication rate in Alloderm versus Surgimend (31.7% versus 44.2%) 2. Patient demographic, risk factors, concurrent therapy for Surgimend and Alloderm 3. Uni- and multivariate analysis 4. Cost analysis
Salzberg et al.[4]	1. Retrospective cohort; nonrandomized	Strattice	Noncomparative	105 Breasts	41.3 mo	1. Total complication rate in Salzberg (8.6%) 2. Types and incidence of complications associated with Strattice. 3. Histological analysis of implanted Strattice.
Dikmans et al.[27]	1. Randomized control trial	Strattice	One-stage IBBR with ADM (Strattice).. Two-stage IBBR without Strattice	91 Breasts	24 mo	1. Total complication (30.8%) 2. Types and incidence of complications associated with 1-stage and 2-stage IBBR. 3. Quality of life at 1 y.
Dikmans et al.[7]	1. Retrospective cohort 2. Nonrandomized.	Strattice	Noncomparative	110 Breasts	2010–2014	1. Total complication (81.8%) 2. Types and incidence of complications associated with single-stage reconstruction with Strattice ADM 3. Reintervention.
Reitsamer et al.[29]	1. Prospective cohort	Strattice	Noncomparative	22 Breasts	6 mo	1. Total complication rate (2%) 2. Types and incidence of complications. 3. Reintervention rate. 4. Arm mobility/function postsurgery.

(*Continued*)

	Critical Appraisal						
Clear Inclusion Criteria	**Blinded Outcome Assessors**	**Attrition Accounted for**	**Selective Outcome Reporting**	**Funding Bias**	**Ethical or IRB Approval**	**Power Calculation**	**Risk of Bias**
Clear inclusion. Patient evaluation flow chart provided.	No	Yes	Yes	No	Unclear	No	High
11 Patients who underwent skin-sparing or nipple-sparing mastectomy followed by direct-to-implant single-stage immediate breast reconstruction in 2010 and 2011 at 3 university-affiliated centers were included	Yes	Yes	Yes	No	Unclear	No	Low
Clear inclusion. All patients who underwent ADM reconstruction. Consecutive patients.	No	Yes	No	No	No	Yes	Low
Clear inclusion. All the women undergoing immediate prosthetic breast reconstruction between March 2004 and June 2005 were included in the study. Patients undergoing delayed reconstruction were excluded, as were those who had undergone previous reconstruction.	Unclear	Unclear	No	Unclear	Unclear	Yes	High
Clear inclusions; patients who underwent implant-based breast reconstruction at a single university medical center between January 1, 2006, and May 1, 2011	Unclear	Yes	No	Unclear	Unclear	Yes	Low
Clear inclusions; patients who had undergone breast reconstruction using saline implant devices and HADM as tissue supplements from 2003 to 2004	Unclear	Unclear	Yes	Unclear	No	No	High
Consecutive patients.; patients undergoing implant-based breast reconstruction with Alloderm or Surgimend between 2005 and 2010	Unclear	Yes	Yes	No	No	Yes	Low
Clear inclusion- immediate single-stage or 2-stage implant-based breast reconstruction with the assistance of Strattice were included in this study	No	Not clear	Yes	No	Not stated	No	High
Clear inclusion. Eligible women were older than 18 y with breast carcinoma or a gene mutation linked with breast cancer who intended to undergo skin-sparing mastectomy and immediate IBBR	Yes	Yes	Yes	No	Yes	Yes	Low
No clear inclusion/exclusion.	No	Not stated	Yes	No	Not stated	No	High
No clear inclusion criteria.	Not stated	No	No	No	Not required	No	High

(*Continued*)

Table 1. (*Continued*)

References	Study Demographics					
	Study Design	Type of ADM	Comparator ADM	Sample Size	Follow-up Stated	Outcome Reported
Lardi et al.[23]	1. Retrospective cohort. 2. Nonrandomized.	Strattice	Noncomparative	200	22.2 mo	1. Total complication rate (43.5%) 2. Types and incidence of complications.
Hille-Betz et al.[25]	1. Retrospective cohort 2. Randomized	Strattice	Immediate expander implant. Delayed expander-implant reconstructions Revision surgery for implant associate breast deformities.	98	19.6	1. Total complication rate (34.7%) 2. Potential impact of subsequent radiotherapy.
Gunnarsson Gl et al.[26]	1. Retrospective cohort 2. Nonrandomized	Strattice	Noncomparative	76	326 d	1. Total complication rate (19.7%) 2. Comparison of complication rate between smokers and nonsmokers; hypertensive and nonhypertenisve patients. 3. Effect of chemoradiotherapy on surgical reconstruction.
Evgeniou et al.[22]	1. Retrospective cohort	Strattice	Noncomparative	21	2009–2011	1. Total complication rate (95.2%) 2. Types and incidence of complications. 3. Complication postradio/chemotherapy.
Glasberg and Light[19]	1. Retrospective cohort 2. Nonrandomized	Strattice	Alloderm	144 Breasts in Strattice	18.2	1. Types and incidence of complications between comparator groups. 2. Histological analysis of samples between comparator groups
Ball et al.[5]	1. Retrospective cohort 2. Nonrandomized	Strattice	1. IBBR using Strattice. 2. IBBR using Surgimend	119 (30 Strattice versus 89 Surgimend)	380 d	1 Total complication rate (25.8%) 2. Types and incidence of complications between comparator groups
Himsl et al.[8]	1. Retrospective cohort	Strattice	Noncomparative	27 Breasts	Median 19 mo	1. Total complication rate (18.5%) 2. Aesthetic outcome—patient reported. 3. Types and incidence of complications between comparator groups
Eichler et al.[11]	1. Retrospective cohort 2. Nonrandomized	Surgimend	1. IBR using Surgimend. 2. IBR using Epiflex.	63 Breasts	2008–2013	1. Total complication rate (17.5%). 2. Types and incidence of complications between comparator groups.
Eichler et al.[20]	1. Retrospective cohort 2. Nonrandomized	Surgimend	1. IBR using Surgimend. 2. IBR using Tutomesh.	18 Surgimend 27 Tutomesh	2014–2016	1. Total complication rate (11.1%). 2. Types and incidence of complications between comparator groups.
Gaster et al.[2]	1. Prospective cohort	Surgimend	No comparators	17	2009–2011	1. Total complication rate (5.9%) 2. Types and incidence of complications. 3. Histological analysis of tissue specimens.

(*Continued*)

Table 2. Patient Demographics, Risk Factors, and Indications for Surgery between ADM Groups

Study Demographics	Alloderm	Strattice	Surgimend
No. patients, n	983	691	617
No. breasts, n	1,659	999	912
Mean BMI (kg/m^2)	25.8	24.35	23.9
Smoking, n	91	112	56
Diabetes, n	46	12	8
Indications for surgery			
Invasive	899	125 patients + 438 breasts	112 patients + 468 breasts
Prophylactic	720	46 patients + 303 breasts	7 patients + 292 breasts
Revision	1	0	0
Delayed	1	0	6 patients

IRB, Institutional Review Board (IRB); IBBR, Implant-based breast reconstruction; IBR, Immediate breast reconstruction.

Table 3. One-way ANOVA between ADM Groups

Complications	Surgimend (n = 912)	Strattice (n = 999)	Alloderm (N = 1,659)	One-way ANOVA (*P* between Groups)
Major (%)	3.51	*2.10*	3.80	0.502
Minor (%)	4.17	**4.60**	3.44	0.693
Seroma (%)	4.61	**8.61**	*3.07*	0.279
Hematoma (%)	*1.21*	2.10	**2.11**	0.580
Implant loss (%)	4.50	**5.61**	*2.59*	0.343
Capsular (%)	*0.00*	0.80	**1.21**	0.345
Total complications (%)	17.98	**23.82**	*16.21*	

P of < 0.05 = significant difference in results. Italics indicates best outcome. Bold indicates worst outcome.

	Critical Appraisal						
Clear Inclusion Criteria	Blinded Outcome Assessors	Attrition Accounted for	Selective Outcome Reporting	Funding Bias	Ethical or IRB Approval	Power Calculation	Risk of Bias
No clear inclusion/exclusion	No	Yes	Yes	No	Not required	No	High
Clear inclusion	No	Not stated	Yes	No	Not stated	No	Fair
Inclusion criteria: the indication was oncologic in 49 cases and prophylactic in 10 cases. No clear exclusion criteria.	No	Yes	No	No	Not stated	No	High
Yes- all patients included had implant-based IBR using strattice.	No	No	Yes	No	Not stated	No	High
Clear inclusion	No	Yes	Yes	No	Not stated	No	Fair
1 Inclusion criteria—patients who underwent IBBR following oncological or prophylactic mastectomy. 2. Exclusion criteria mentioned.	No	No	Unclear	No	No	No	High
No clear inclusion/exclusion criteria	No	No	No	No	Not stated	No	High
Yes	No	Yes	No	No	Not stated	No	High
Yes	No	Not stated	Yes	No	Yes	No	Fair
Yes	No	Yes	Yes	No	Yes	No	Fair

CI, 5.79–17.83%), and 12.5% (95% CI, 7.92–17.08%), respectively. The rate of hematoma was relatively low and consistent with a pooled complication rate of 2.10%, 2.11%, and 1.21% in Strattice, Alloderm, and Surgimend, respectively in Figure 6.

The incidence rates for localized inflammation or erythema were irregular in the use of Strattice, Alloderm, and Surgimend as seen in Figure 7. The occurrence of capsular contracture in Table 3 showed that Alloderm was the highest at 1.21% (95% CI, 0.68–1.73%) compared with Strattice (0.80%; 95% CI, 0.25–1.35%). There were no reported cases of capsular contracture associated with the use of Surgimend in the searched articles.

DISCUSSION

ADM-assisted breast reconstruction provides better esthetic outcome when compared with the traditional subpectoral implant placement, in terms of creating a better inframammary fold definition and allowing for lower rate of capsular contracture.[30] In this meta-analysis, the performance of ADMs within in vivo models and how well this compared with human studies were also investigated.

A known complication in implant-based breast reconstruction following skin-sparing mastectomy is skin necrosis. It ranges from simple epidermolysis to a full-thickness flap necrosis, and if severe enough, lead to implant exposure, and subsequent implant loss.[3] Although this outcome was not included in our study because

Table 4. Bonferroni Statistical Analysis within Groups using SPSS

Dependant Variables							
Significance Value		Major Infection	Minor Infection	Seroma	Hematoma	Implant Loss	Capsular Contracture
Fixed Variable	Brand	*P* Sig.	*P* Sig.	*P* Sig.	*P* Sig.	*P* Sig.	*P* Sig.
Strattice	Alloderm	0.745	1	1	0.91	0.667	1
	Surgimend	1	1	0.346	1	0.651	1
Alloderm	Strattice	0.745	1	1	0.91	0.667	1
	Surgimend	1	1	0.858	1	1	0.448
Surgimend	Strattice	1	1	0.346	1	0.651	1
	Alloderm	1	1	0.858	1	1	0.448

$P < 0.05$ = significant difference in values. (Sig. = *P* value)

Table 5. Surgimend Group Pooled Complication

Complications	n	p (%)	SE	95% CI
Major	32	3.51	0.0061	2.31–4.70
Minor	38	4.17	0.0066	2.87–5.46
Seroma	42	4.61	0.0069	3.24–5.97
Hematoma	11	1.21	0.0036	0.50–1.91
Implant loss	41	4.50	0.0069	3.15–5.84
Capsular	0	0.00		
Total complications	164	17.98	0.0127	15.49–20.47
Total	912			

p, Proportion; SE, standard error.

Table 6. Strattice Group Pooled Complications

Complications	n	p (%)	SE	95% CI
Major	21	2.10	0.0045	1.21–2.99
Minor	46	4.60	0.0066	3.30–5.90
Seroma	86	8.61	0.0089	6.87–10.35
Hematoma	21	2.10	0.0045	1.21–2.99
Implant loss	56	5.61	0.0073	4.18–7.03
Capsular	8	0.80	0.0028	0.25–1.35
Total complications	238	23.82	0.0135	21.18–26.47
Total	999			

p, proportion; SE, standard error.

Table 7. Alloderm Group Pooled Complication

Complications	n	p (%)	SE	95% CI
Major	63	3.80	0.0047	2.88–4.72
Minor	57	3.44	0.0045	2.56–4.31
Seroma	51	3.07	0.0042	2.24–3.90
Hematoma	35	2.11	0.0035	1.42–2.80
Implant loss	43	2.59	0.0039	1.83–3.36
Capsular	20	1.21	0.0027	0.68–1.73
Total complications	269	16.21	0.0090	14.44–17.99
Total	1,659			

p, proportion; SE, standard error.

Table 8. Incidence of Localized Inflammation between ADMs

Types of ADMs	Breast, n (%)	SE	95% CI
Surgimend (n = 912)	10 (1.10)	0.0034	0.0042–0.0177
Strattice (n = 999)	33 (3.3)	0.0057	0.022–0.0441
Alloderm (n = 1,659)	37 (2.2)	0.0036	0.0152–0.0294
Total number of incidence	80 (2.24)		

SE, standard error.

ADMs do not directly cause skin/flap necrosis, this will be discussed further. Studies report various methods to improve cellular behavior through surface modifications of ADMs including chemical modification with L-arginine in bovine ADM[31] and modification of porcine acellular dermal matrix PADM via dopamine self-polymerization/collagen immobilization.[32] A recent in vivo rat study further showed chemical cross-linking Permacol, which is porcine-derived, with hexamethylene diisocyanate caused an increase in cellular density and penetration at 12 months postimplantation compared with noncrosslinked implants. Furthermore, it was suggested that a thorough assessment of postmastectomy skin flap viability is crucial to reduce the incidence of skin necrosis.[23,27]

Capsular contracture is thought to be a local inflammatory response leading to excessive production of collagen by fibroblasts where they are in contact with the implant.[33] The Baker Classification system is a subjective classification system based upon clinical findings in the patient. Studies have proven that the use of ADMs in implant-based breast reconstruction is associated with a lower rate of capsular contracture up to a 20-fold reduction.[34] Basu et al.[35] reported a significant reduction in granulation tissue formation, levels of vascular proliferation, chronic inflammatory changes, fibroblast cellularity and foreign body giant cell inflammatory reaction, when comparing acellular cadaveric dermis sample to native breast capsules. Cross correlation with cytotoxicity studies in animal models reveal similar results. The degree of inflammation caused by human ADMs at 4 weeks in an in vivo rabbit model for incisional hernia repair was not statistically different from that caused by the use of porcine ADMs.[36] In both instance, the degree of inflammation detected by histology was low grade (level 1). A further study looked at the inflammatory response induced by porcine ADMs that were prepared by ultrasonification and freeze-thawing. Inflammatory markers, Interleukin-2 (IL-2) and Interferon gamma (IFN-y), were absent in both the PADM and human acellular dermal matrix group up to 48 hours postimplantation.[37] These are produced by antigen-sensitized T-cells in the context of foreign body rejection,[38] suggesting both were well tolerated. There may be a role for biopsy during a single-stage ADM breast reconstruction to ascertain local tissue inflammation through definitive histological analysis. This is especially necessary as capsular contracture itself can be influenced by other confounding factors.[34,39]

Although pooled data showed that Surgimend has the highest incidence of infection (7.68%), when individualized, Alloderm has the highest rate of major infections (3.8%) when compared with Surgimend (3.51%) and Strattice (2.1%). Although the HADM, Alloderm is clas-

Table 9. Regression Analysis of Outcome and Confounding Effects on All ADM Groups using SPSS

	Regression Significance (*P*)								
Complications	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**
Major infection	0.966	0.991	0.973	0.973	0.821	0.876	0.869	0.926	0.957
Minor infection	0.346	0.072	0.065	**0.034**	0.063	0.116	0.191	0.249	0.234
Seroma	0.168	0.385	0.228	0.339	0.28	0.411	0.546	0.578	0.696
Hematoma	0.247	0.358	0.241	0.308	0.428	0.303	0.426	0.33	0.65
Implant loss	0.315	0.594	0.473	0.547	0.558	0.54	0.625	0.693	0.787
Capsular contracture	0.535	0.669	0.647	0.802	0.863	0.8	0.842	0.909	0.717

P< 0.05 indicates statistical significance. Bold indicates statistical significance *p*<0.05

a, Predictors: (Constant), Brand; b, Predictors: (Constant), Brand, Smoking; c, Predictors: (Constant), Brand, Smoking, Obesity; d, Predictors: (Constant), Brand, Smoking, Obesity, Diabetes_Mellitus; e, Predictors: (Constant), Brand, Smoking, Obesity, Diabetes_Mellitus, Age; f, Predictors: (Constant), Brand, Smoking, Obesity, Diabetes_Mellitus, Age, Neoadjuvant_Chemo; g, Predictors: (Constant), Brand, Smoking, Obesity, Diabetes_Mellitus, Age, Neoadjuvant_Chemo, Adjuvant_Chemo; h, Predictors: (Constant), Brand, Smoking, Obesity, Diabetes_Mellitus, Age, Neoadjuvant_Chemo, Adjuvant_Chemo, Preop_radiotherapy; i, Predictors: (Constant), Brand, Smoking, Obesity, Diabetes_Mellitus, Age, Neoadjuvant_Chemo, Adjuvant_Chemo, Preop_radiotherapy, Postop_radiotherapy.

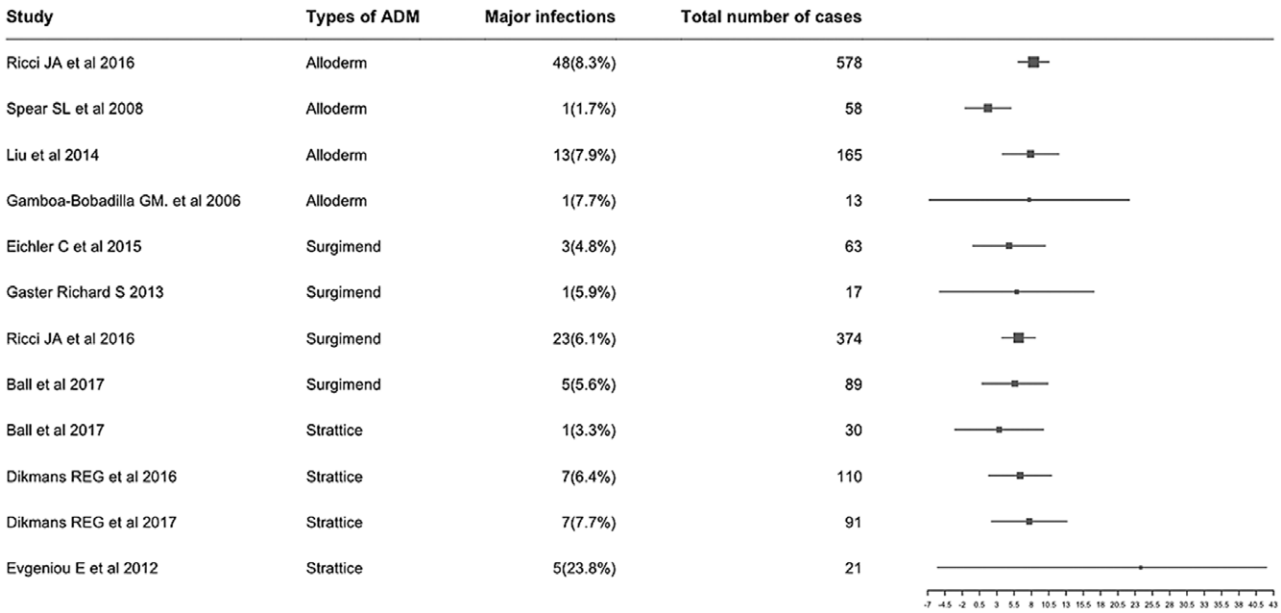

Fig. 2. Forest plot estimating the proportion of the incidence of major infection among Alloderm, Surgimend, and Strattice groups.

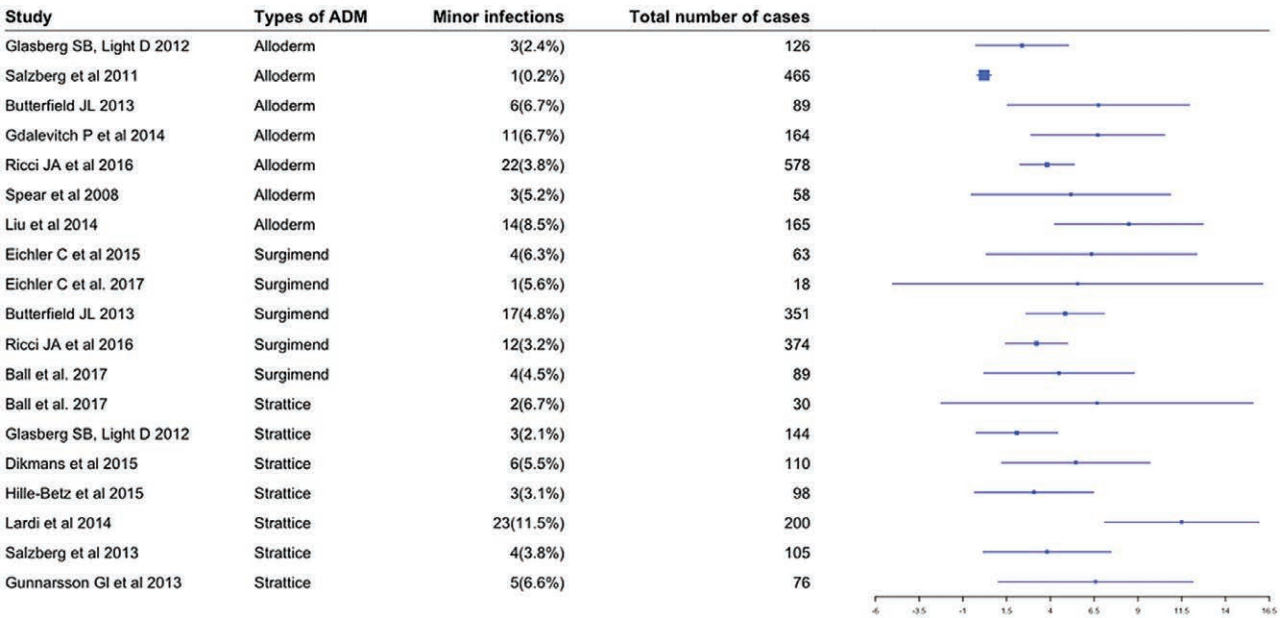

Fig. 3. Forest plot estimating the proportion of the incidence of minor infections among Alloderm, Surgimend, and Strattice groups.

Study	Types of ADM	Seroma	Total number of cases
Butterfield JL 2013	Alloderm	14(15.7%)	89
Glasberg SD, Light D 2012	Alloderm	27(21.4%)	126
Gdalevitch P et al 2014	Alloderm	17(10.4%)	164
Ricci JA et al 2016	Alloderm	13(2.2%)	578
Spear et al 2008	Alloderm	1(1.7%)	58
Liu et al 2014	Alloderm	5(3.0%)	165
Gamboa-Bobadilla, G. M. et al 2006	Alloderm	1(7.7%)	13
Eichler C et al 2015	Surgimend	1(1.6%)	63
Butterfield JL 2013	Surgimend	30(8.5%)	351
Ricci JA et al 2016	Surgimend	7(1.9%)	374
Ball et al. 2017	Surgimend	4(4.5%)	89
Ball et al. 2017	Strattice	3(10%)	30
Glasberg SD, Light D 2012	Strattice	9(6.25%)	144
Dikmans et al 2016	Strattice	23(20.9%)	110
Hille-Betz et al 2015	Strattice	20(20.4%)	98
Lardi et al 2014	Strattice	21(10.5%)	200
Salzberg et al 2013	Strattice	2(1.9%)	105
Gunnarsson GI et al 2013	Strattice	2(2.6%)	76
Evgeniou, E. et al 2012	Strattice	4(19.0%)	21
Himsl I et al 2012	Strattice	2(7.4%)	27

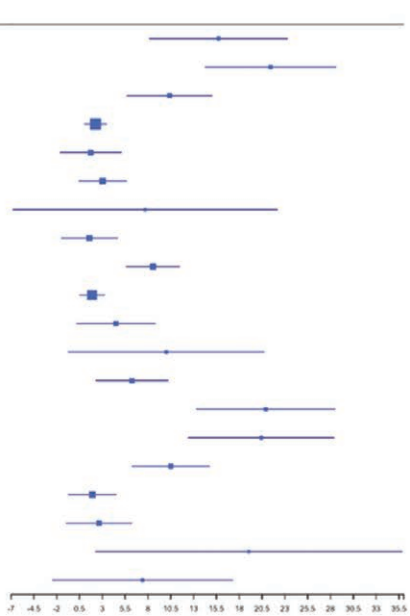

Fig. 4. Forest plot estimating the proportion of the incidence of seroma among Alloderm, Surgimend, and Strattice groups.

Study	Types of ADM	Implant loss	Total number of cases
Salzberg et al 2011	Alloderm	6(1.3%)	466
Glasberg SB, Light D 2012	Alloderm	3(2.4%)	126
Butterfield JL 2013	Alloderm	10(11.2%)	89
Ricci JA et al 2016	Alloderm	17(2.9%)	578
Spear SL et al 2008	Alloderm	1(1.7%)	58
Liu et al 2014	Alloderm	8(4.8%)	165
Gamboa-Bobadilla, G. M. et al 2006	Alloderm	1(7.7%)	13
Butterfield JL 2013	Surgimend	29(8.3%)	351
Ricci JA et al 2016	Surgimend	10(2.7%)	374
Ball et al. 2017	Surgimend	2(2.2%)	89
Dikmans REG et al 2015	Strattice	13(11.8%)	110
Glasberg SB, Light D 2012	Strattice	2(1.4%)	144
Hille-Betz et al 2015	Strattice	4(4.1%)	98
Lardi et al 2014	Strattice	25(12.5%)	200
Dikmans REG et al 2017	Strattice	2(2.2%)	91
Salzberg et al 2013	Strattice	4(3.8%)	105
Evgeniou, E. et al 2012	Strattice	5(23.8%)	21

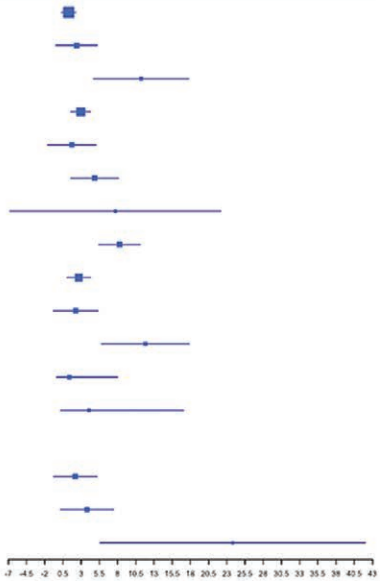

Fig. 5. Forest plot estimating the proportion of the incidence of implant loss among Alloderm, Surgimend, and Strattice groups.

sified as aseptic, histologic studies have reported neovascularization and inflammatory cell penetration into both sterile and aseptic ADMs[40] Nahabedian[41] has demonstrated that Alloderm was able to revascularize, recellularize and following tissue integration, able to tolerate mild-to-moderate infections. AlloDerm showed greater microvascular density and soft-tissue ingrowth.[42]

With regard to high incidence of seroma rate in Strattice group, Hille-Betz et al.[25] report that there was no antibiotic irrigation intraoperatively in their study, whereas the study by Dikmans et al.[7] stated that there was a lack of registration on the use of antibiotics. In the study by Butterfield 2012,[10] Surgimend had a much lower seroma rate as compared with Alloderm. The author reported that the number of drains inserted and whether the ADM is fenestrated or unfenestrated should be taken into consideration. Lardi et al.[23] have also suggested that the rate or seroma could potentially be reduced by lowering the drain removal threshold to around < 20 cc/24 h. Multiple studies have suggested that with the use of antibiotics for a period of time, 2 bulb suction drains, and by reducing the dead space between implant/expanded with skin, the incidence of seroma formation could potentially be reduced.[23]

Study	Types of ADM	Hematoma	Total number of cases
Salzberg et al 2011	Alloderm	5(1.1%)	466
Glasberg SB, Light D 2012	Alloderm	2(1.6%)	126
Gdalevitch P et al 2014	Alloderm	3(1.8%)	164
Ricci JA et al 2016	Alloderm	6(1.0%)	578
Liu et al 2014	Alloderm	3(1.8%)	165
Eichler C et al. 2017	Surgimend	1(0.5%)	18
Butterfield JL 2013	Surgimend	4(1.1%)	351
Ricci JA et al 2016	Surgimend	5(1.3%)	374
Ball et al. 2017	Surgimend	1(1.1%)	89
Ball et al. 2017	Strattice	2(6.7%)	30
Dikmans REG et al 2016	Strattice	3(2.7%)	110
Reitsamer R, Peintinger F 2014	Strattice	1(4.5%)	22
Hille-Betz et al 2015	Strattice	2(2.0%)	98
Lardi et al 2014	Strattice	10(5%)	200
Dikmans REG et 2017	Strattice	3(3.3%)	91

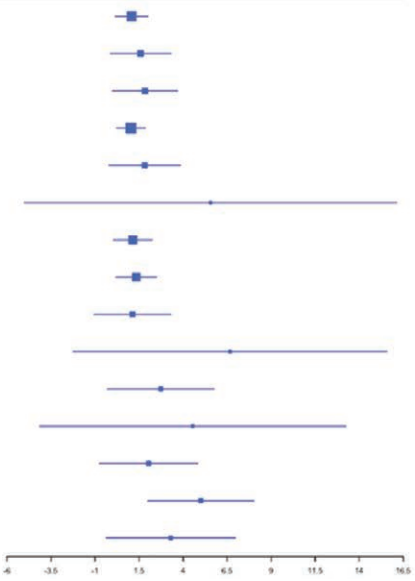

Fig. 6. Forest plot estimating the proportion of the incidence of hematoma among Alloderm, Surgimend, and Strattice groups.

Study	Types of ADM	Localized inflammation	Total number of cases
Eichler C et al 2015	Surgimend	3(4.8%)	63
Eichler C et al. 2017	Surgimend	3(16.7%)	18
Ball et al. 2017	Surgimend	4(14.5%)	89
Ball et al. 2017	Strattice	5(16.7%)	30
Dikmans REG et al 2016	Strattice	16(14.5%)	110
Dikmans REG et al 2017	Strattice	5(5.5%)	91
Glasberg SB, Light D 2012	Strattice	7(4.9%)	144
Glasberg SB, Light D 2012	ALloderm	11(8.7%)	126

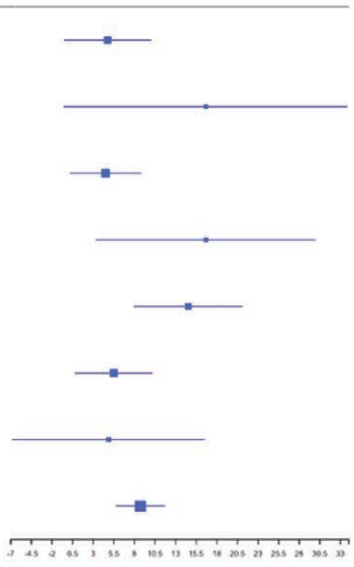

Fig. 7. Forest plot estimating the proportion of the incidence of localized inflammation among Alloderm, Surgimend, and Strattice groups.

Localized inflammation or erythema is also known as red breast syndrome, whose etiology is still poorly understood. It was thought to be a delayed hypersensitivity reaction to ADMs in breast reconstruction,[43] causing redness to the skin overlying the ADMs. Salzberg et al.[34] have reported that there is no evidence of true rejection response on histological analysis.

Multiple studies suggested that the main factors leading to an increase in complication rate are age older than 50 years, smoking status, mastectomy weight of > 600 g, and BMI > 30.[34,44] A couple of articles also showed that breast irradiation postoperatively is related to a higher rate of complication, including wound dehiscence, higher rate of infections, and possibly capsular contraction.[34,41] However, as discussed, there were no significant difference when adjusting for confounding factors. Inevitably, due to the lack of individual data from each study during extrapolation of data, we are unable to be completely advocate these accuracy as it might lead to a bias in results.

There were some limitations in this study. One of the main weaknesses is the low level of evidence in the studies included. We were only able to include 1 randomized controlled trial and 3 prospective cohort studies. It was also difficult to compare statistical differences in the indication for surgery as there were a few studies that re-

corded the number of patients instead of the number of breasts. In quite a few studies, we were not able to extract data on patient's comorbidities such as smoking and diabetic status. We also acknowledge that most of our studies have high risk of bias as reported in Table 1.

From the thorough analysis, Strattice exhibited a slightly higher overall pooled complication rate compared with Alloderm and Surgimend. However, the incidence of individual complication varies between studies. Potential learning curve effects of using ADMs may affect the outcome. A cost analysis and a large prospective study of different ADMs may aid in choosing the type of ADMs to be used.

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