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McGill University Health Centre

Technology Assessment Unit

of the McGill University Health Centre (MUHC)

Evaluation of Acellular Dermal Matrix for Breast Reconstruction: An Update

An update of the TAU report (published May 5, 2009) entitled "Clinical efficacy and cost of Allogenic Acellular Dermal Matrix (AADM) in implant-based breast reconstruction of post mastectomy cancer patients

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EXECUTIVE SUMMARY

Background: Acellular dermal matrix (ADM) is used in breast reconstruction surgery with the goal of increasing implant expansion and capsular reinforcement, and generally improving aesthetic outcomes. There is a concern that ADM could increase the likelihood of infection as it is a foreign body and some preparations are not sterilised. It is relatively expensive, costing $2000 per breast. A previous report by the Technology Assessment Unit (TAU) in 2009 reviewed ADM use and recommended temporary use for 60 patients on the condition that a record would be maintained of the risk factors for poor outcomes, perioperative and post-operative complications, and subsequent revision procedures and that the aesthetic outcome of each procedure be formally evaluated.

Objective: The purpose of this report is to update the previous review of the literature on ADM use for breast reconstruction and to summarize the data on infection rate and aesthetic outcomes recorded at the McGill University Health Centre (MUHC).

Methods: We carried out a systematic literature review using online databases of the medical literature and databases of health technology assessment reports published before November 1, 2011. Besides information on study design and patient characteristics, we also extracted estimates of the risk of various complications and results of aesthetic outcome measurements when available. We also carried out meta-analyses of the risk of infection, and of the risk ratio of infection with and without ADM use. The latter analysis used results from the sub-group of studies that included a control cohort in whom ADM was not used. Finally, we directly addressed 7 North American and European centres in an attempt to determine whether they found ADM satisfactory for use in breast reconstructive surgery.

Results: We found 17 individual articles and three systematic reviews published since 2009. Two of the three systematic reviews concluded there is an increased complication rate with the use of ADM. The third systematic review of ADM cohorts concluded that capsular contraction rates were lower using ADM, and that rates of minor acute complications were comparable to the rates in large cohort studies of breast reconstruction in which ADM was not used. There were no randomized controlled studies. Most studies (14/17) used a retrospective cohort design and the remainder used a prospective cohort design; 9 articles included a control cohort in which ADM was not used. The pooled risk (95% confidence interval) of any complication following ADM use in the reconstruction process was 20.8% (15.3, 27.7). The pooled risk of individual complications was as follows: Exposure with implant loss 10.6%, infection with implant removal 4.1%, infection without implant removal 6.1%, hematoma 2.5%, seroma 6.9%, skin necrosis 6.5%, capsular contracture 3.4% and cellulitis 5.4%. The meta-analysis of risk ratios suggested that

ADM was associated with a higher risk of implant loss, infection without implant removal and seroma. ADM was associated with a lower risk of capsular contracture. Some of these studies identified risk factors (e.g. increasing age, obesity, prior radiation therapy) that increase the risk of complications following ADM use.

Though most studies alluded to better aesthetic outcome following ADM use, only 3 studies attempted to quantify it. One study found that ADM improved the post-operative appearance of the breast compared to the pre-operative appearance. A second study measured patient satisfaction but found no significant difference between ADM and non-ADM groups. A third study found that breasts reconstructed with ADM scored higher in terms of the overall reconstruction as well as the final outcome of the inframammary fold, compared to breasts reconstructed without ADM.

Of the centres directly questioned about their current use of ADM, four responded. ADM was reportedly used in 15%, 25% and 70% of immediate implant-based reconstructions at three of the centres(1-3). In the fourth centre the rate of use varied according to the surgeon concerned – 5% for one surgeon and 95% for another. One centre reported that complication rates with and without ADM were comparable. Another reported that the aesthetic benefits were greatest for the sub-group of women with large, ptotic breasts(3).

At the MUHC, data were collected on 71 two-stage reconstructions (45 patients) in which ADM was used between December 2008 and January 2010. The total complication rate was 16.9%. There was no assessment of the aesthetic outcome. The estimated risk of individual complications was lower or comparable with the pooled risk estimated from the literature, though the confidence intervals around the estimates were very wide owing to the small sample size.

CONCLUSIONS

- Based on observational studies, the evidence suggests that there is a higher risk of exposure of the breast implant, infection, seroma, and higher overall complication rates for two-stage breast reconstruction with ADM. However, contemporary experience at the MUHC and at one other centre that was consulted does not confirm an association between ADM use and higher complication rates.

- The available evidence suggests that the risk of capsular contracture appears to be lower and aesthetic outcomes superior with the use of ADM for breast reconstruction following cancer surgery. The quality of this evidence is poor. However, objective evidence on aesthetic outcome is difficult to collect and it is possible that no better evidence will be developed.

RECOMMENDATIONS

There is evidence (limited in quantity and quality) to support the claim that use of ADM results in superior aesthetic outcomes, but the evidence from the literature suggests that use of ADM may be associated with a higher rate of clinically significant complications. However, limited experience at the MUHC does not support this. Accordingly, the committee recommends that this material should be temporarily approved for breast reconstruction at the MUHC, but only in the context of a continuing prospective cohort study in which risk factors (age, BMI, diabetes, radiation), and relevant outcomes (length of hospital stay, frequency of additional operations), and aesthetic results are documented. These data should be reviewed at 6 and 12 months and decisions on the permanent use of ADM decided in the light of this evidence.

SOMMAIRE

Contexte

La matrice dermique acellulaire (MDA) est utilisée dans la chirurgie de reconstruction du sein dans le but d'augmenter l'expansion de l'implant, le renforcement capsulaire et de façon générale, pour améliorer les résultats esthétiques. Un doute persiste à l'effet que la MDA pourrait augmenter la probabilité d'infections puisqu'il s'agit d'un corps étrangé qui n'est pas toujours stérile. Ceci est relativement dispendieux, au coût de

2 000 $ par sein. Un rapport précédent de l'Unité d'évaluation des technologies (Technology Assessment Unit (TAU)) produit en 2009, a examiné l'utilisation de la MDA et a recommandé son utilisation temporaire pour 60 patients à la condition qu'un dossier soit tenu concernant les facteurs de risque en regard des résultats médiocres, les complications préopératoires, post-opératoires ainsi que les procédures de révisions, et enfin, une évaluation formelle des résultats esthétiques de chaque procédure.

Objectif

Le but de ce rapport est de faire une mise à jour de la revue de littérature précédente sur l'utilisation de la MDA lors de la reconstruction mammaire et de faire un résumé des données relatives au taux d'infection et des résultats esthétiques notés au Centre universitaire de santé McGill (CUSM).

Méthodologie

Nous avons fait une revue systématique de la littérature à partir des bases de données de la littérature médicale et des rapports d'évaluation des technologies publiés avant le 1er novembre 2011. Outre les informations sur la conception des études et des données patients, nous avons aussi recueilli les estimations du risque des différentes complications ainsi que les données des résultats esthétiques lorsque disponibles. Nous avons aussi effectué des méta-analyses du risque d'infection et du rapport de risque d'infection, avec et sans l'utilisation de la MDA. Enfin, nous avons contacté directement 7 centres nord-américains et européens dans le but de connaître leur taux de satisfaction sur l'utilisation de la MDA lors de la reconstruction mammaire.

Résultats

Nous avons identifié 17 articles originaux et 3 revues systématiques publiés depuis 2009. Deux des trois revues systématiques ont conclu qu'il y a une augmentation du taux de complications découlant de l'utilisation de la MDA. La troisième revue systématique conclut que les taux de contraction capsulaire étaient plus faibles lors de l'utilisation de la MDA et que les taux de complications mineures aigues étaient comparables à ceux des études de cohortes importantes de reconstruction mammaire où la MDA n'était pas utilisée. Aucune étude aléatoire ne fut trouvée. La plupart des études (14/17) étaient fondées sur des cohortes rétrospectives et les autres, sur des cohortes prospectives; 9 articles incluaient une cohorte contrôle où la MDA n'était pas utilisée. Le risque sommatif (95% intervalle de confiance) de toute complication découlant de l'utilisation de la MDA dans le procédé de reconstruction était de 20,8% (15,3 - 27,7%). Le risque sommatif des complications individuelles était le suivant: protrusion avec perte de l'implant (10,6%); infection avec extraction de l'implant (4,1%); infection sans extraction de l'implant (6,1%); hématome (2,5%); sérome (6,9%); nécrose de la peau (6,5%); contraction capsulaire (3,4%) et cellulite (5,4%). Les méta-analyses des rapports de risque suggérèrent que la MDA était associée à un risque plus élevé de perte de l'implant, d'infection sans extraction de l'implant et de sérome. La MDA était associée à un plus faible risque de contraction capsulaire. Quelques unes de ces études ont identifié des facteurs de risque (ex.: âge avancé, obésité, sessions de radiothérapie) qui augmentent le risque de complications associées à l'utilisation de la MDA.

Bien que la plupart des études faisaient allusion à de meilleurs résultats esthétiques suite à l'utilisation de la MDA, seulement 3 études ont tenté de les quantifier. Une étude a trouvé que la MDA améliorait l'aspect post-opératoire des seins comparé à l'aspect préopératoire. Une seconde étude a évalué la satisfaction des patientes mais n'a trouvé aucune différence significative entre les groupes avec MDA et sans MDA. Enfin, une troisième étude a souligné que la reconstruction mammaire avec la MDA obtenait un meilleur pointage que sans la MDA en termes de reconstruction globale et du résultat final au niveau du pli inframammaire.

Seulement quatre des centres questionnés sur leur utilisation actuelle de la MDA ont donné suite à notre demande. La MDA était ainsi utilisée chez 15%, 25% et 70% des reconstructions mammaires à partir d'implants chez trois de ces centres (1-3). Chez un quatrième centre, le taux d'utilisation variait selon le chirurgien (5% pour un chirurgien et 95% pour un autre). Un centre rapporta que les taux de complications avec et sans MDA étaient comparables. Un autre centre mentionna que les avantages esthétiques

étaient plus importants chez le sous-groupe des femmes avec de gros seins montrant une ptose mammaire (3).

Au CUSM, les données furent colligées à partir de 71 reconstructions à deux phases (45 patientes) chez qui la MDA fut utilisée entre les mois de décembre 2008 et janvier 2010. Le taux global de complications était de 16,9%. Il n'y avait pas d'évaluation des résultats esthétiques. Le risque estimé des complications individuelles était plus faible ou comparable aux risques sommatifs estimés dans la littérature, même si les intervalles de confiance de ces estimés étaient très larges dus au faible échantillonnage.

Conclusion

- Découlant des études d'observation, les preuves suggèrent que les risques sont plus importants au niveau de la protrusion de l'implant mammaire, des infections, des séromes ainsi que d'un plus haut taux de complications globales pour la reconstruction mammaire en deux phases avec la DMA. Cependant, l'expérience actuelle au CUSM ainsi qu'à un autre centre consulté ne confirme pas un lien entre la MDA et un taux plus important de complications.
- Les preuves disponibles suggèrent que le risque de contraction capsulaire semble plus faible et les résultats esthétiques, supérieurs, avec l'utilisation de la MDA pour la reconstruction mammaire suivant une chirurgie pour cancer La qualité de ces preuves est cependant faible. En contre partie, les preuves objectives des résultats esthétiques sont difficiles à colliger et il est possible qu'aucune meilleure preuve ne sera disponible.

Recommandation

Il existe des preuves (peu nombreuses et de faible qualité) pour supporter la revendication selon laquelle l'utilisation de la MDA entraîne des résultats esthétiques supérieurs, mais les preuves tirées de la littérature suggèrent que l'utilisation de la MDA pourrait être associée à un plus grand risque de complications cliniques importantes. Cependant, l'expérience limitée du CUSM en cette matière ne supporte pas l'énoncé précédent. Par conséquent, le comité recommande que ce matériel devrait être approuvé de façon temporaire pour la reconstruction mammaire au CUSM, mais seulement dans le contexte d'une étude prospective continue où les facteurs de risque (âge, indice de masse corporelle, diabète, radiation), les résultats pertinents (durée d'hospitalisation, nombre de chirurgies additionnelles) ainsi que les résultats esthétiques sont documentés. Ces données devraient être révisées après 6 et 12 mois et la décision de l'utilisation permanente de la MDA devrait être faite à la lumière des preuves recueillies.

LIST OF ABBREVIATIONS

ADM	Acellular Dermal Matrix
BMI	Body Mass Index
MUHC	McGill University Health Centre
TAU	Technology Assessment Unit

Evaluation of Acellular Dermal Matrix: An update

1. BACKGROUND

Acellular dermal matrix (ADM) is an immunologically inert dermal matrix derived from cadaveric human skin. It is used increasingly in breast reconstruction (4). ADM acts as a scaffold or sling covering and supporting the inferior and lateral aspect of the breast pocket(5). Using ADM to define the breast-shaped subpectoral pocket can result in good inferior pole projection and inframammary fold definition(6). In addition, the increased support provided by ADM can prevent contour deformities, implant rippling, and bottoming out, giving an overall better aesthetic outcome(6).

There is a possibility that using ADM, a foreign body, will increase the risk of an infection(7). Other complications, with rates that are higher than standard reported rates for non-ADM reconstruction have been reported. These include implant exposure with loss of implant, infection, partial flap necrosis, and seroma formation(4).

In 2009, the Technology Assessment Unit (TAU) published a report on the clinical efficacy and cost of ADM in implant-based postmastectomy breast reconstruction(8). The TAU recommended temporary approval of the technology at the MUHC for 60 patients(8) on condition that, a record be kept for all patients undergoing breast reconstruction with ADM, in particular with respect to the risk factors for poor outcomes, perioperative and post-operative complications, and subsequent revision procedures and that the aesthetic outcome of each procedure be evaluated(8).

During the year 2011-2012, one piece of ADM was used at the Montreal General Hospital, 17 pieces at the Lachine Hospital, and 40 pieces at the Royal Victoria Hospital. The estimated cost of ADM is $2,000 per piece amounting to a total cost of $116,000 for the year 2011-2012.

2. OBJECTIVES

- To update our systematic review on complication rates and aesthetic outcomes following the use of ADM for breast reconstruction in mastectomy patients with studies published since 2009.
- To analyse data that have accrued on patients who have undergone postmastectomy breast reconstruction using ADM at the MUHC.

3. METHODS

3.1 Literature search and study selection

A systematic literature review to identify systematic reviews or clinical research studies was performed using the online medical literature databases Medline and Embase, the Cochrane library and databases of health technology assessment reports (INAHTA, CADTH, CRD, INESSS). The literature search in the previous TAU report ended in February 2009. This updated search was performed to include articles published after February 2009. There was no language limit applied. The key word and MeSH term “acellular dermal matrix” was used. The date of the final literature search was November 9, 2011. One reviewer (IN) performed the literature search and screened records. Two authors (IN and XX) determined the eligibility of studies for inclusion.

3.2 Eligibility criteria

Clinical research studies on the use ADM for breast or nipple reconstructive surgeries published in peer-reviewed articles were included if they fulfilled the following inclusion criteria: i) had a sample size of at least 20 patients, ii) the participants had undergone prophylactic or oncologic mastectomy surgery, and iii) the postmastectomy reconstructive surgery was breast or nipple reconstruction. We included studies published from 2009 to 2011 in English or in French.

3.3 Data collection process and data analysis

The following variables were extracted from the included studies when available: ADM brand (Alloderm or Dermamatrix), study design (prospective or retrospective cohort), type of surgical procedure performed (i.e. one stage or two-stage reconstruction), length of patient follow-up, sample size, population characteristics, range and mean (median) age of participants, ADM and non-ADM surgery complications, aesthetic outcomes, overall study conclusion and extent of manufacturer’s support for the research. All authors reviewed all included studies. One author (IN) extracted and analysed the data from the included studies. The data extraction was verified by a second author (XX). We estimated the pooled risk of the most commonly reported complications across studies (exposure with implant loss, infection, hematoma, seroma, partial skin necrosis, capsular contracture, cellulitis) using a random effects meta-analysis model. We estimated the pooled risk ratio of each complication associated with ADM based on results from studies that included a control cohort in which ADM was not used. For the meta-analyses we used eligible studies from our earlier report in addition to those identified by the current review. Descriptive statistics and graphs were obtained using Microsoft Excel and Stata(9).

In studies that included a non-ADM control group, we assessed whether the ADM and non-ADM study groups were comparable by looking at the differences in BMI,

smoking, diabetes and radiation therapy, which we considered to be important risk factors for complications. We considered a mean difference of 5 years in age or 5 units of BMI to be clinically important. For the remaining variables, which were all measured as dichotomous variables, we considered the imbalance between the groups to be clinically important if the risk ratio was outside of the range from 0.8 to 1.25. In each case we compared the two ends of the confidence interval of the mean difference or ratio of the proportion with the risk factor to the clinically important value.

3.4 Tool for assessing risk of bias

We assessed the risk of bias in studies that compared ADM to non-ADM. The assessment was performed using an adapted version of the Downs and Black Checklist for determining the risk of bias in observational studies(10). The Downs and Black Checklist was developed in 1998 and consists of 27 items divided into five categories: Reporting, External validity, Bias, Confounding, and Power(10). This checklist has high internal consistency, good test-retest and inter-rater reliability, as well as good face validity(10).

We adapted this scale to create a version that included only 6 items that were pertinent to this report (See Appendix 1). Our adapted checklist assessed:

- selection bias (were ADM and non-ADM patients comparable and were they recruited from the same population?)
- detection bias (were hospital charts assessed in a blinded manner and was follow-up for at least 2 weeks?)
- confounding (was there an imbalance in important risk factors?), and
- manufacturer's financial support (did the manufacturer support the project in a way that could signify conflict of interest?).

The "No" and "Not reported (NR)" answers were summed and recorded as "number of items with potential bias."

3.5 Expert opinion survey on the value of ADM in immediate breast reconstruction

We contacted 10 plastic surgeons at 7 major American and European centres. In total, we contacted 5 North American centres, which were the University of British Columbia, Toronto General Hospital, University of Virginia, University of California, and Stony Brooke University. In addition, 2 centres in Manchester and Bradford, UK, were contacted.

The 10 surgeons had previous experience performing post-mastectomy breast reconstruction surgery. The survey was based on four questions: 1) whether the experts have used ADM in immediate breast reconstruction at their institute; 2) in what percentage of patients is it used; 3) have they found ADM satisfactory; 4) it is a consensus among their colleagues that ADM significantly improves the aesthetic outcome, at least in a sub-group of patients.

4. RESULTS

4.1 Results of literature search

Our initial search of the electronic databases and the health technology databases produced 306 records. Following title and abstract screening, 47 records were selected for full text screening. There were 29 studies that did not meet the inclusion criteria and were excluded from the review for the following reasons: 16 articles were letters, case studies, or viewpoints; 4 studies had less than 20 patients; 4 articles had non-cancer patients; 4 did not perform breast or nipple reconstruction surgery; and 1 study did not use ADM. In total, we identified 17 new studies and 3 systematic reviews. None of the studies identified used a randomized, controlled design.

4.2 Summary of previous systematic reviews and meta-analyses

We found 3 recent systematic reviews published since 2010 (11-13). Two systematic reviews (11;13) concluded that there is an increase in complication rates associated with ADM use. The third systematic review, which did not use a meta-analysis(12), concluded that capsular contraction rates were lower using ADM, and that rates of minor acute complications were comparable to the rates in studies not using ADM. In addition, the systematic review by Newman et al. (13) mentioned the need for strict patient selection criteria to reduce complications. The conclusions of the systematic reviews are summarized in Table 1. None of the systematic reviews included results from controlled studies that compared ADM and non-ADM cohorts.

4.3 Characteristics of studies included in the systematic review

Table 2 summarizes some of the study design and patient characteristics of the 17 new studies identified by our review compared to our previous report. Of these 4 (14-17) were not previously identified in other systematic reviews or HTAs. The majority of studies (13 [76.5%]) were retrospective cohort studies. Three studies(18-20) were prospective cohorts. There were ten studies(5-7;21-27) that compared ADM with non-ADM patients. The sample size of the studies ranged from 20 patients to 2121 patients. The number of breast reconstructions ranged from 29 to 3063.

Of the 17 included studies, 12(70.6%), (5;6;18;19;21-28) used two-stage reconstruction as their surgical procedure for positioning implants. Four

studies(7;14;20;29) used one-stage reconstruction and one study(30) used both types of reconstruction. All but two studies (6;28) used Alloderm as the brand of ADM in the implant-based reconstruction surgeries. One study(28) used FlexHD and the other study(6) used both FlexHD and Strattic.

The mean follow-up time ranged from 3 to 29 months. The mean age of participants in the included studies ranged from 46.2 to 57 years. Information on support from the manufacturer was not reported in 3(16.7%) studies. Seven(41.2%) studies(5;18-20;25;27;29) reported potential conflicts of interest such as: the authors(20;29) were paid consultants for the manufacturer, the article was a result of contract research(19) or the authors belong to the company's speakers bureau and were paid lecturers(5;18;25;27). Seven(41.2%) studies stated explicitly that they did not receive support from the manufacturer.

4.4 Risk of complications following ADM use

Table 2 lists in detail the types and risks of different complications in each study. Two studies(19;30) did not mention any complications, though it was unclear whether complications were not reported or whether there were none to report.

4.4.1 Complications in one-stage ADM reconstructions

Among the three studies(14;20;29) that reported complications in one-stage ADM reconstructions, overall complication rates ranged from 3.9% to 11.5%. The implant exposure rate ranged from 0.6%-5%, the hematoma rates from 1%-1.3% and infection rates from 0.2% to 6.4%. The rate of capsular contraction was reported to be 0.4% in the study by Salzberg et al.

4.4.2 Complication rates of two-stage reconstructions with ADM and without ADM

Four articles(31-34), from our previous report, also provided information on the risk of complications following ADM use in two-stage reconstructions. Table 4 lists the pooled risk of different types of complications across studies together with the confidence and prediction intervals. When the prediction interval is much wider than the confidence interval it indicates high heterogeneity in risk between studies.

The pooled risk of any complication following breast reconstruction with ADM was 20.8%. The pooled risk of individual complications ranged from 2.5% (for Hematoma) to 10.6% (for exposure of the breast implant). There was considerable heterogeneity between studies for most types of complications.

Figures 1a-1i lists the results of the meta-analyses comparing the risk of infection in ADM and non-ADM groups. In addition to the 9 studies identified by the current search, we considered 1 study that was included in our previous report. The risk of exposure of the breast implant, risk of infection (without implant loss) and risk of

seroma were statistically significantly higher in the ADM group. The risk of capsular contracture was lower in the ADM in the two studies that reported this outcome.

4.4.3 Comparison of complication rates in irradiated and nonirradiated breasts using ADM

Four studies(20;25;26;28) listed the types and rates of complications in irradiated breasts. The study by Salzberg(20) and colleagues compared results on 21 irradiated breasts (11 of which were irradiated before ADM reconstruction and 10 breasts after ADM reconstruction) to the complete cohort of 466 breasts. The overall complication rates were 14.3% for all irradiated breasts compared to 3.9% overall. The risk of skin breakdown was the most common complication associated with irradiation after reconstruction (20%). Implant malposition (9.1%) was the only complication found in breasts irradiated before reconstruction.

Nguyen(26) and colleagues carried out 97 irradiated reconstructions, 69 of which used ADM and 28 reconstructions that did not use ADM. An equal percentage of ADM and non-ADM irradiated patients (1.0%) were readmitted as a result of infection. The rate of explantation due to infection, seroma, or extrusion was 3.1% in the ADM group and 0% in the non-ADM group.

The study by Nahabedian(25) et al. included 9 patients who underwent radiation preoperatively and 14 patients who were irradiated postoperatively, both groups using ADM. The number of incisional dehiscences was the highest out of all complications in patients who were irradiated preoperatively(22.2%). In patients who were irradiated preoperatively, the number of seromas(15.4%) was the most common complication. When comparing nonirradiated to irradiated reconstructions, there were more complications (infections, seromas, skin necrosis) in the nonirradiated group.

The third study to discuss complications was by Rawlani et al(28). In this study there were 26 breasts reconstructed with ADM that underwent radiation therapy. The overall complication rate for the irradiated breasts was 30.8%, which was much higher than the rate of 13.7% in the nonirradiated breasts.

In brief, two studies(20;26) compared irradiated breasts with and without the use of ADM. The other two studies compared irradiated and nonirradiated ADM breasts and found that the risk of complications was higher in the irradiated breasts than the nonirradiated breasts. However, there is insufficient evidence to make any conclusions.

4.5 Risk of bias assessment of studies comparing ADM to a control group

We assessed the risk of bias (Table 5) in the 10 observational studies (5;6;21-27;35) that were included in any of the meta-analyses in Figures 1a-1i. Five of the studies had at least four items out of six indicating potential bias.

The majority of studies did not have comparable ADM and non-ADM groups, and did not adjust for confounding factors (Table 5). The least reported items were follow-up duration and blinded assessment of outcomes. Table 6 lists the comparisons between the ADM and non-ADM group on the risk factors. In four studies the percentage of patients who received radiation was higher in the ADM group, thus potentially increasing the risk of an adverse outcome in the ADM group. On the other hand, in four studies the percentage of smokers was lower in the ADM group and in three studies the mean age was lower in the ADM group, thus possibly decreasing the risk of an adverse outcome in this group. The average BMI was higher in ADM patients in one study, while the percentage of patients with diabetes was higher in ADM patients in two studies.

4.6 Aesthetic outcomes

We found only three articles(5;24;29) that measured aesthetic outcomes following ADM use. In the study by Cassileth et al.(29) aesthetic evaluation was performed by 20 evaluators using pre- and postoperative photos. Thus each patient served as their own control. Half the evaluators were surgical residents and the other half was drawn from the general population. Each evaluator rated each photo based on a four-point scale (excellent, good, fair, poor). All identifying marks were removed from the photos before rating. They concluded that the postoperative photos scored higher than the pre-operative photos, and that ADM use was associated with a statistically significant aesthetic improvement compared to the pre-operative appearance of the breast.

Hanna(24) and colleagues assessed patient satisfaction by administering a telephone questionnaire on a five-point scale, from 1 being very dissatisfied to 5 being very satisfied. Of the 75 patients included in the study, 45.3% (34) completed the phone questionnaire. The authors did not find a statistically significant difference between the 16 patients in the ADM group vs. the 18 patients in the non-ADM groups in the mean scores measuring patient satisfaction (overall satisfaction 3.6 vs. 3.3, shape of reconstruction 3.8 vs. 3.4 and ease of the expansion experience 3.9 vs. 3.7).

The third study to assess aesthetic outcome was by Vardanian(5) and colleagues. They evaluated two cosmetic outcomes: aesthetics of the overall reconstruction and the aesthetics of the final outcome of the inframammary fold. They compared 208 ADM breasts to 129 non-ADM breasts. The evaluation was performed by rating

photos of the final reconstruction. Frontal and oblique views were rated on a four-point scale, 1 being a poor result and 4 being excellent, by a blinded panel of four individuals - a surgeon, a secretary, and two medical students. Scores for both the overall aesthetic outcome and the aesthetic outcome of the inframammary fold were statistically significantly higher in the ADM group ($p<0.05$). In addition, the aesthetic outcome of the inframammary fold was statistically significantly higher in the ADM group ($p<0.05$).

4.7 Results from the expert opinion survey

Four(1-3;36) of the 10 experts we contacted responded to our survey. The surgeons were from Toronto General Hospital, University of Virginia, University Hospital South Manchester, UK, and Stony Brooke University. The experts reported using ADM in 15%, 25% and 70% of immediate implant-based reconstructions at three of the centres(1-3). In the fourth centre ADM was used by one surgeon in 5% of patients, while another surgeon used it in 95% of cases. The centre in UK reported that complication rates with and without ADM were comparable(36). The Stony Brooke centre reported that the aesthetic benefits were greatest for the sub-group of women with large, ptotic breasts(3).

5. ADM USE AT THE MUHC

Prospective data were collected by Dr. Karl Schwarz, a plastic surgeon at the MUHC, who uses ADM (DermaMatrix) in all breast reconstruction surgeries. Dr. Schwarz collected data on 46 patients (73 breast reconstructions) who underwent two-stage reconstruction surgery with ADM following mastectomy. The variables that we used for analysis included: number of revisions following completion of reconstruction, patient's age, type of complication, and whether radiation therapy was used.

Patients were entered into the cohort from December 2008 to July 2010. Second surgery complication data was not documented for 9 of the 46 patients due to the ongoing scheduling of second surgeries. The remaining 37 patients had been followed for at least 3 months following the second surgery. The median age of the patients was 48 with a range of 21 to 70 years old.

Overall, there were 12 complications and three of them required revisions (Table 4). Two revisions were due to implant malposition, and the third one because of the implant size causing rippling. There was also one case of implant loss due to infection. Four breasts underwent pre-operative radiation and 2 breasts had post-operative radiation, none of which had any complications. The risk of complications tended to be lower or comparable to the pooled risks estimated from our literature review (see Table 4). However, because of the small numbers with wide confidence intervals any conclusions on this issue must be considered tentative. No attempt was

made to systematically estimate the aesthetic benefit of ADM in this cohort of patients.

6. DISCUSSION

Acellular Dermal Matrix (ADM) has emerged as a tool in breast-reconstruction surgeries to reduce the risk of aesthetic complications such as capsular contracture and implant rippling. The increase in the number of publications on this subject since our last report reflects the growing interest in this technology. However, the high cost (~$2,000 per breast) and concerns regarding risk of infection has limited uptake.

We identified 17 observational (cohort) studies that have studied the risk of common complications in following ADM use in breast reconstruction surgery. Based on 10 of these studies, which included a control group among whom ADM was not used, it appears that there is an increased risk of a number of complications (exposure with implant loss, infection without implant removal and seroma). Some of these studies (2,3,11,12) concluded that ADM should only be used in a carefully selected subset of patients because there appear to be well defined predictors of complications following ADM use (e.g. increasing age, obesity, prior radiation therapy) as well as predictors of better aesthetic outcomes (e.g. larger, ptotic breasts). In the small cohort of patients treated at the MUHC, the risk of complications was either lower than or within the confidence limits of the pooled estimate of risk across all studies of two-stage reconstructions.

A recent abstract from a group that had previously reported increased risk of seroma and infection rates following ADM use (22), provided results at the 90th meeting of the American Association of Plastic Surgeons on whether implementation of specific procedural modifications minimized complications when using ADM (37).The authors found that clinical measures, including draining the sub-mastectomy and sub-ADM planes, adding post-operative soft compression dressings, and using surgical bras, can minimize the rates of complications associated with the use of ADM (37).

It should be noted that a limitation of our analysis comparing outcomes in ADM and non-ADM groups is that the results are not adjusted for possible confounding. Due to the observational design of these studies we cannot eliminate the possibility that an imbalance of important risk factor variables, between the ADM and non-ADM groups explained the observed difference in outcomes. It is also possible that there was systematic difference in the level of skill of surgeons carrying out the non-ADM vs. ADM procedures. Individual surgeons typically do not carry out both types of procedures.

7. CONCLUSIONS

- The available evidence suggests that the risk of capsular contracture appears to be lower and aesthetic outcomes superior with the use of ADM for breast reconstruction following cancer surgery. The quality of this evidence is poor. However, objective evidence on aesthetic outcome is difficult to collect and it is possible that no better evidence will be developed.
- Based on observational studies, the evidence suggests that there is a higher risk of exposure of the breast implant, infection, seroma, and higher overall complication rates for two-stage breast reconstruction with ADM. However, contemporary experience at the MUHC and at one other centre that was consulted does not confirm an association between ADM use and higher complication rates.

RECOMMENDATION

There is evidence (limited in quantity and quality) to support the claim that use of ADM results in superior aesthetic outcomes, but the evidence from the literature suggests that use of ADM may be associated with a higher rate of clinically significant complications. However, limited experience at the MUHC does not support this. Accordingly, the committee recommends that this material should be temporarily approved for breast reconstruction at the MUHC, but only in the context of a continuing prospective cohort study in which risk factors (age, BMI, diabetes, radiation), and relevant outcomes (length of hospital stay, frequency of additional operations), and aesthetic results are documented. These data should be reviewed at 6 and 12 months and decisions on the permanent use of ADM decided in the light of this evidence.

Table 1 Summary of systematic reviews and meta-analyses

Study (year) (reference)	Total No. of studies	Conclusions
Israeli et al. (2011) (11)	7	• AlloDerm can be safely combined with adjuvant radiotherapy • AlloDerm does not increase postoperative complications beyond what would be expected with radiotherapy alone
Jansen et al. (2011) (12)	14	• Rates of minor acute complications (i.e. wound infection, hematoma, seroma, and minor skin necrosis) are comparable to two-stage non AlloDerm alloplastic reconstruction complication rates • AlloDerm may show a lower risk of capsular contraction
Newman et al. (2010) (13)	12	• Significant short-term complication rate with human ADM • Appropriate patient selection, modification of intraoperative technique, and adjustments in postoperative protocols may reduce ADM complications

Table 2 Characteristics of included cohort studies

Study (year) (reference)	Study design	Reconstruction type	Follow-up (months) [Range]	Sample size (# patients) [# breasts]	Age (years) [Range]	Conflict of interest
Cassileth et al. (2011) (29)	Cohort	One-stage	Mean 19 months [Range 6-43]	43 [78 breasts]	Mean 57 years [Range 26-73]	[1]Yes
Collis et al. (2011) (23)	Retrospective cohort	Two-stage	NR	105 [174 breasts] ADM group: 63 [106 breasts] Non-ADM: 42 [68 breasts]	ADM: mean 53±11 years Non-ADM: mean 53±11 years	None
Hanna et al. (2011) (24)	Retrospective cohort	Two-stage	ADM: 7.7±7.9 months Non-ADM: 9.6±6.7 months	75 ADM group: 31[38 breasts] Non-ADM: 44[62 breasts]	ADM: 47.3±6.9 years Non-ADM: 54.7±8.2 years	None
Liu et al. (2011) (7)	Retrospective matched cohort	One-stage and two-stage	3 months	343 [470 breasts] ADM group: 192 [266 breasts] Non-ADM: 151 [204 breasts]	*NR	None
Rawlani et al. (2011) (28)	Retrospective cohort	Two-stage	11±6.6 months	84 [121 breasts]	Mean 50.2 years [Range 26-81]	None
Salzberg et al. (2011) (20)	Prospective cohort	One-stage	28.9±21.3 months [Range 0.3-97.7]	269 [466 breasts]	NR	[2]Yes

Vardanian et al. (2011) (5)	Retrospective cohort	Two-stage	Mean 29 months	203 [337 breasts] ADM group: 123 [208 breasts] Non-ADM: 80 [129 breasts]	ADM: mean 49±11 years Non-ADM: 47±10 years	[3]Yes
Antony et al. (2010) (21)	Retrospective cohort	Two-stage	NR	2121 [3063 breasts] ADM: 96 [153 breasts] Non-ADM: 2025 [2910 breasts]	ADM: median 44.5 [Range 28-79] Non-ADM: median 48.1 [Range 18-88]	None
Basu et al. (2010) (19)	Prospective cohort	Two-stage	NR	20	Mean 47 years [Range 33-64]	[4]Yes
Chun et al. (2010) (22)	Retrospective cohort (chart review)	Two-stage	NR	283 [415 breasts] ADM: 269 breasts Non-ADM:146 breasts	ADM: mean 47±10.5 years Non-ADM: mean 46.2±8.4 years	None
Lanier et al. (2010) (6)	Retrospective cohort	Two-stage	ADM: 6.67±2.75 months Non-ADM: 7.82±4.51 months	119 [127 breasts] ADM : 52 breasts Non-ADM : 75 breasts	ADM : 51±9.6 years Non-ADM : 50±8.6 years	None
Nguyen et al. (2010) (26)	Retrospective cohort	Two-stage	NR	204 [321 breasts] ADM group: 41 [75 breasts] Non-ADM: 163 [246 breasts]	Overall mean: 47.9 years [Range 25-72] ADM: mean 49.1 years Non-ADM: mean 47.7 years	NR
Derderian et al. (2009) (14)	Retrospective cohort	Immediate one-stage	NR	20	NR	NR
Haddock et	Retrospective chart review	One-stage and two-	NR	49 (72 breasts)	NR	NR

al. (2009)(30)		stage				
Nahabedian et al. (2009) (25)	Retrospective cohort	Two-stage	ADM group: 17 months [Range 6-37]	361 [476 breasts] ADM group: 76 [100 breasts] Non-ADM: 285 [376 breasts]	48.2 years [Range 17-77] ADM: mean 46 range 23-69	[5]Yes
Namnoum et al. (2009) (18)	Prospective cohort	Two-stage	21 months [Range 3-32]	20 [29 breasts]	NR	[6]Yes
Sbitany et al. (2009) (27)	Retrospective cohort	Two-stage	NR	100 [176 breasts] ADM group: 50 [92 breasts] Non-ADM: 50 [84 breasts]	ADM: 48.6±8.6 years Non-ADM: 51.7±12.8 years	[7]Yes

*NR-Not reported. Footnote: Seven studies did not report a mean follow-up time and two studies mentioned separate follow-up times for the ADM and non-ADM groups, but not for the entire study population.
[1]L.C. is a paid consultant for LifeCell and Allergan; [2] A.S. is a consultant for LifeCell Corporation; [3]C.C. is a member of the speaker's bureau for LifeCell Corporation; [4]C.B.B serves on the speakers bureau for LifeCell Corp., and received research grant funding from LifeCell for consumables for this project; [5]M. N. is a member of the speakers bureau for LifeCell Corporation and lectures on the use of AlloDerm and Strattice for breast and abdominal wall reconstruction; [6]J.N. is a member of the Speaker's Bureau for LifeCell Corporation; [7]H. N. L. is a member of the speaker's bureau for LifeCell Corporation.

Table 3 Complication rates in the included cohort studies (rates were calculated based on the number of breasts)

Study (year) (reference)	Sample size	One-stage reconstruction	Two-stage reconstruction	
		ADM	ADM	Non-ADM
Cassileth et al. (2011) (29)	# breasts: N=78	Overall complication 11.5% Hematoma 1.3% Seroma 6.4% Infection 6.4% Mastectomy flap necrosis with reoperation 3.8%	-	-
Collis et al. (2011) (23)	# breasts: ADM N=106; Non-ADM N=68		§Total complications 18.9% Infection with removal 5.7% Epidermolysis13.2%	§Total complications 7.4% Infection with removal 4.4% Epidermolysis1.5%
Hanna et al. (2011)* (24)	# breasts: ADM N=40; Non-ADM N=62		§Total complications 41.9% Minor complications 19.4% Seroma 19.4% Hematoma 9.7% Cellulitis 6.5% Skin necrosis 6.5% Major complications 22.6% Explant 16.1% Infection without removal 32.2%	§Total complications 38.6% Minor complications 29.5% Seroma 13.6% Hematoma 4.5% Cellulitis 18.2% Skin necrosis 6.8% Wound separation 6.8% Major complications 9% Explant 4.5% Infection without removal 9%
Rawlani et al. (2011) (28)**	# breasts: N=121		§Total complication 16.5% Soft tissue infection 7.4% Flap necrosis 6.6% Seroma 1.7%	

			ADM Exposure 6.6%	
Salzberg et al. (2011) (20)**	# breasts: N=466	§Complication rate 3.9% Implant loss 1.3% Skin necrosis 1.1% Hematoma 1.1% ADM Exposure 0.6% Capsular contracture 0.4% Infection 0.2% Implant exposure 0.2% Implant malposition 0.2%		
Vardanian et al. (2011) (5)	# breasts: ADM N=208; Non-ADM N=129		§Total complications 29.3% Capsular contracture 3.8% Bottoming out 4.8% Inframmary fold problems 8.2% Rippling 3.8% Seroma/hematoma 2.4% Infection/wound 2% Shift 1.9%	§Total complications 40.3% Capsular contracture 19.4% Bottoming out 12.4% Inframmary fold problems 19.4% Rippling 10.9% Seroma/hematoma 1.6% Infection/wound 2.3% Shift 9.3%
Antony et al. (2010) (21)	# breasts: ADM N=153; Non-ADM N= 2910		§Total complications 23.6% Seroma 7.2% Cellulitis 3.9% Reconstructive failure 5.9% Infection with removal 3.3% Hematoma 2.0% Flap necrosis 4.6% Leak/failed expansion 0%	§Total complications 12.4% Seroma 1.6% Cellulitis 1.4% Reconstructive failure 1.9% Infection with removal 1.3% Hematoma 0.9% Flap necrosis 6.5% Leak/failed expansion 0.1%
Chun et al.	# breasts: ADM N=269; Non-		ADM infection rate 8.9%	Non ADM infection rate 2.1%

(2010) (22)	ADM N=146		Necrosis 23.4% Seroma 14.1% Hematoma 2.2%	Necrosis 8.9% Seroma 2.7% Hematoma 1.4%
Lanier et al. (2010) (6)	# breasts: ADM N=52; Non-ADM N=75		§Total complications 46.2% Infection 28.9% Skin necrosis 15.4% Seroma 15.4% Capsular contracture 3.9% Tissue expander explantation 19.2% Reoperation 25% Hematoma 0%	§Total complications 22.7% Infection 12% Skin necrosis 5.3% Seroma 6.7% Capsular contracture 5.3% Tissue expander explantation 5.3% Reoperation 8% Hematoma 0%
Nguyen et al. (2010) ** **(26)**	# breasts: ADM N=75; Non-ADM N=246		Infection rate 5.3% Explantation rate 8.0%	Infection rate 2.8% Explantation rate 1.6%

Liu et al. (2010) (7)	# breasts :
	ADM =266
	Non-ADM =204
		ADM :
		Wound infection 6.8%
		Major infection 4.9%
		Minor infection 1.9%
		Skin necrosis 13.9%
		Seroma 7.1%
		Hematoma 0.4%
		§Complications 19.5%
		
		Non-ADM :
		Wound infection 2.5%
		Major infection 2.5%
		Minor infection 0%		

		Skin necrosis 10.8% Seroma 3.9% Hematoma 0% §Complications 12.3%		
Derderian et al. (2009)* (14)	# patients: N=20	Five (25%) patients had implant exposure due to T-point breakdown.		
Nahabedian et al. (2009) (25)**	# breasts: ADM N=100; Non-ADM N=376		Infection rate 5% Prosthesis removal 2%	Infection rate 5.85% Prosthesis removal 5.32%
Namnoum et al. (2009) (18)	# breasts: ADM N=29		§Total complications 10% Infection requiring device removal 3.4% Marginal necrosis requiring reoperation 3.4% Seroma / non-incorporation 3.4%	
Sbitany et al. (2009) (27)	# patients: ADM N=50; Non-ADM N=50		§Total complications 18% Seroma 6% Cellulitis 8% Infection with expander removal 8%	§Total complications 14% Seroma 6% Cellulitis 6% Infection with expander removal 6%

*Complications reported by patient not breast reconstruction
** Studies comparing complications between irradiated and nonirradiated breasts with ADM
§ Total complications may not add up to the types of complications listed because only the main types of complications were reported in the studies.

Table 4 Comparison of risk of complication (%) associated with two-stage ADM reconstruction at the MUHC vs. the pooled average across 16 studies

Complication	Number (%) of complication at MUHC* (N=71 breasts)		Risk of complication based on systematic review			
		95% Confidence Interval	Number of studies	Pooled risk (%)	95% Confidence Interval	95% Prediction Interval
Any complications	12* (16.9)	9.2, 28.05	11	20.7	15.3, 27.4	7.0, 47.5
Exposure with implant loss/ explantation	1 (1.4)	0.07, 8.65	6	10.1	5.6, 17.6	1.6, 43.2
Infection	1(1.4)	0.07, 8.65	7	With implant removal: 4.1	2.6, 6.2	2.3, 7.1
			11	Without implant removal: 5.3	2.8, 9.5	0.6, 32.2
Hematoma	2 (2.8)	0.5, 10.7	5	2.4	1.0, 5.6	0.3, 19.8
Seroma	1 (1.4)	0.07, 8.65	11	6.8	4.3, 10.6	1.6, 24.4
Partial flap/skin necrosis	1 (1.4)	0.07, 8.65	9	6.6	3.2, 13.1	0.6, 46.9
Capsular contracture	1 (1.4)	0.07, 8.65	4	3.4	1.9, 5.9	0.9, 11.3
Cellulitis	-		3	5.2	2.95, 8.9	0.1, 70.3

* This includes any complications that occurred after the first surgery. Nine patients did not have complete follow-up information after the second surgery.
Footnote: 'Any complication' includes complications besides the types of complications listed in this table and is therefore greater than the sum of the individual complications.

Table 5 Risk of bias in selected observational studies*

	Selection bias		Detection bias		Confounding	Manu-facturer's support	Items with potential bias
	Patients recruited from same population & same time period	Comparable exposed and unexposed groups	Blinded assessment	Follow-up long enough for outcomes to occur#	Adjustment of confounding in analysis	No substantial support	
Collis (2011)(23)	YES	NO	NO	NR	NO	YES	4
Hanna (2011)(24)	YES	NO	NR	YES	NO	YES	3
Vardanian (2011) (5)	NO	NO	YES	YES	YES	NO	3
Antony (2010)(21)	YES	YES	NR	NR	YES	YES	2
Chun (2009)(22)	YES	YES	NR	NR	YES	YES	2
Lanier (2010)(6)	YES	NO	NR	YES	NO	YES	3
Nguyen (2010)(26)	NO	NO	NR	NR	NO	NR	6
Nahabedian (2009)(25)	NO	NR	NR	NR	NO	YES	5
Sbitany (2009)(27)	NO	NO	NR	NR	NO	NO	6
Preminger (2008)(35)	YES	NR	NR	NR	NO	NR	5

* Green: No apparent risk of bias, Yellow: Not possible to evaluate risk of bias, Red: Risk of bias
NR: Not reported #Recovery is usually 2 weeks for two stage breast reconstruction surgery (Spear). In all studies that reported follow-up information, the follow-up was long enough. Therefore, we did not grade whether there were systematic differences in the length of follow-up.

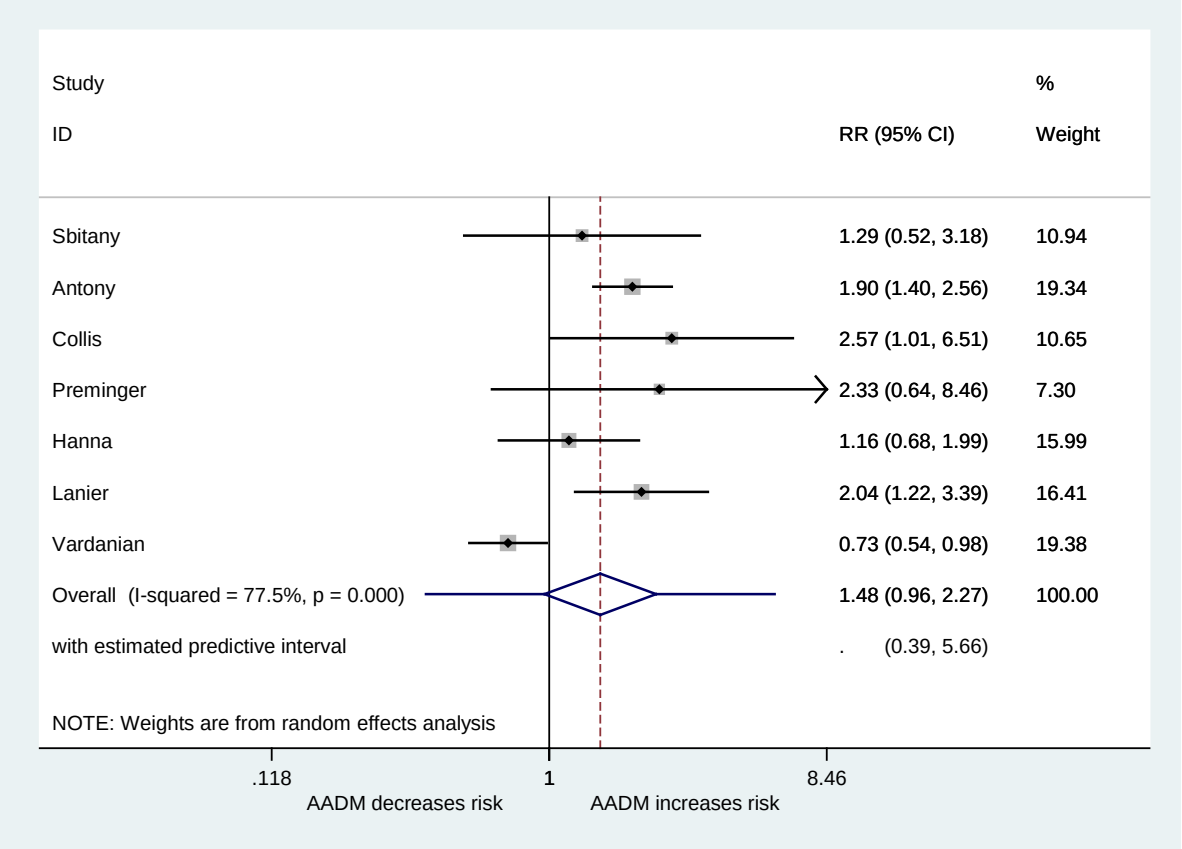
Table 6 Summary of covariate characteristics for ADM and non-ADM comparison studies

	Mean age			Mean BMI			% Smoking			% Diabetes			% Radiation		
Study	**ADM**	**Non-ADM**	**Difference (95%CI)**	**ADM**	**Non-ADM**	**Difference (95%CI)**	**ADM**	**Non-ADM**	**Difference (95%CI)**	**ADM**	**Non-ADM**	**Difference (95%CI)**	**ADM**	**Non-ADM**	**Difference (95%CI)**
Collis (2011)	53	53	0 (-4.3, 4,3)	-	-		-	-					7.9	7.1	0.79 (-13.5, 12.4)
Hanna (2011)	47.3	54.7	-7.4 (-11, 3.8)	28.5	27.4	1.1 (-1.6, 3.8)	12.9	25	-12.1 (-30, -9)	16	18.2	-2 (-20.1, 18.6)	19.3	13.6	5.7 (-12.5, 26)
Vardanian (2011)	49	47	2 (-1.2, 5.2)	23	23	0 (-1.8, 1.8)	4.9	8.7	-3.9 (-13.3, 3.8)		-	-	-	-	-
Antony (2010)	44.5 *	48.1 *	-3.6	23.8	26.3	-2.5 (-3.7, 1.2)	10.4	-	-		-	-	31.2	32.3	-1.1 (-10.2, 9.5)
Chun (2009)	47	46.2	0.8	25.5	23.8	1.7	-	-	-	-	-	-	-	-	-
Lanier (2010)	51	50	1	29.8	24.7	5.1	-	-	-			-	-	-	-
Nguyen (2010)	49.5	47.7	1.4	-	-	-	0	8	-8 (-3.2, 13.5)	7.3	6.7	0.57 (-7, 14.6)	68.3	42.3	26 (7.6, 41.1)
Nahabedian (2009)	46	-	-	-	-	-	-	-	-	-	-	-	30.3	-	-
Sbitany (2009)	48.6	51.7	-3.1 (-7.4, 1.2)	26.4	28.2	-1.8 (-3.0, 0.6)	8	14	-6 (-20.4, 8.4)	6	4	2 (-9.7, 14)	12	8	4 (-10, 18.1)

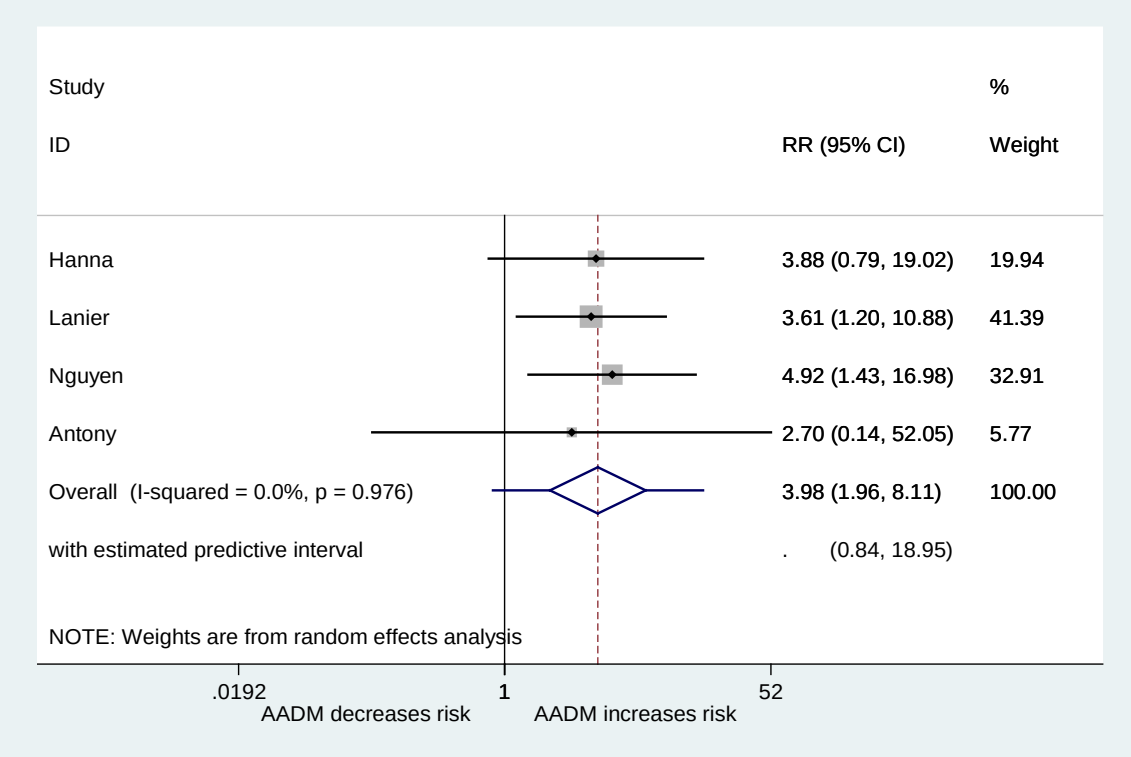
*Median age reported; Footnote: Cells shaded in green imply that the risk of an adverse outcome was lower in the ADM group, while cells shaded in red imply that the risk was higher in the ADM group. The study by Preminger et al.(35) was not included in this table because it did not report any covariate information.

Figures 1(a-i) Forest plots of risk ratios of different complications in two-stage breast reconstruction surgeries comparing groups with and without ADM; a) total complications, b) exposure with implant loss/explantation, c) infection leading to implant loss (major infection), d) minor infection, e) seroma, f) partial flap/skin necrosis, g) capsular contracture, h) cellulitis, i) hematoma.

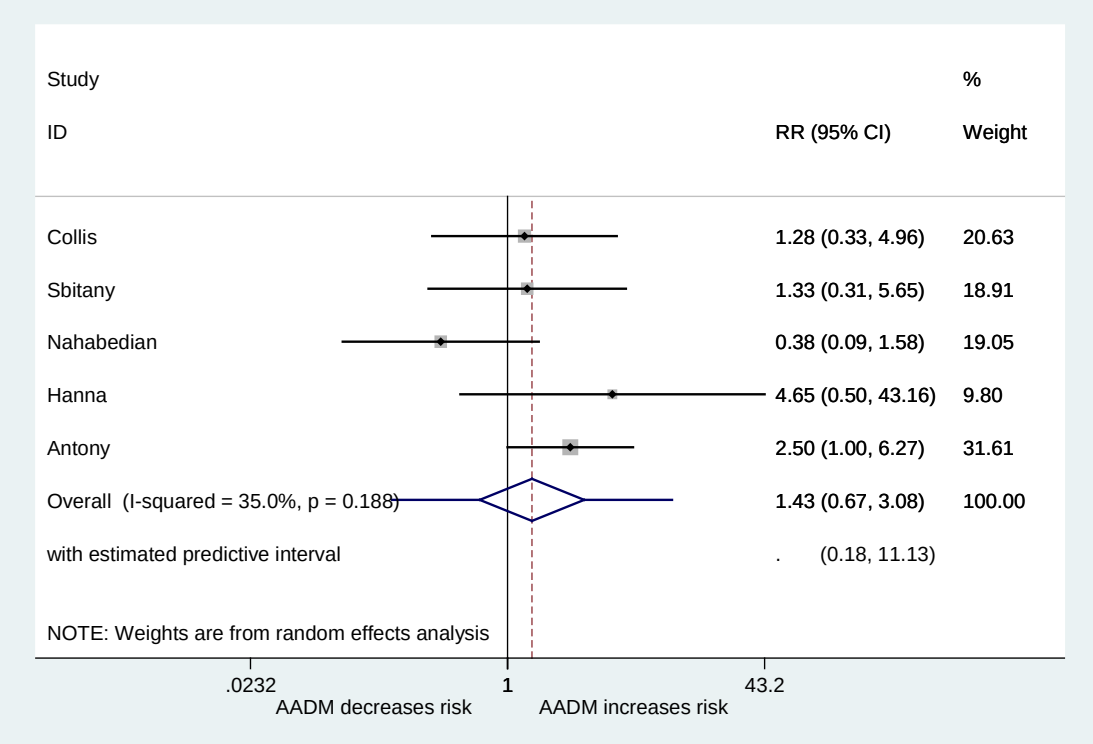
a)Total complications



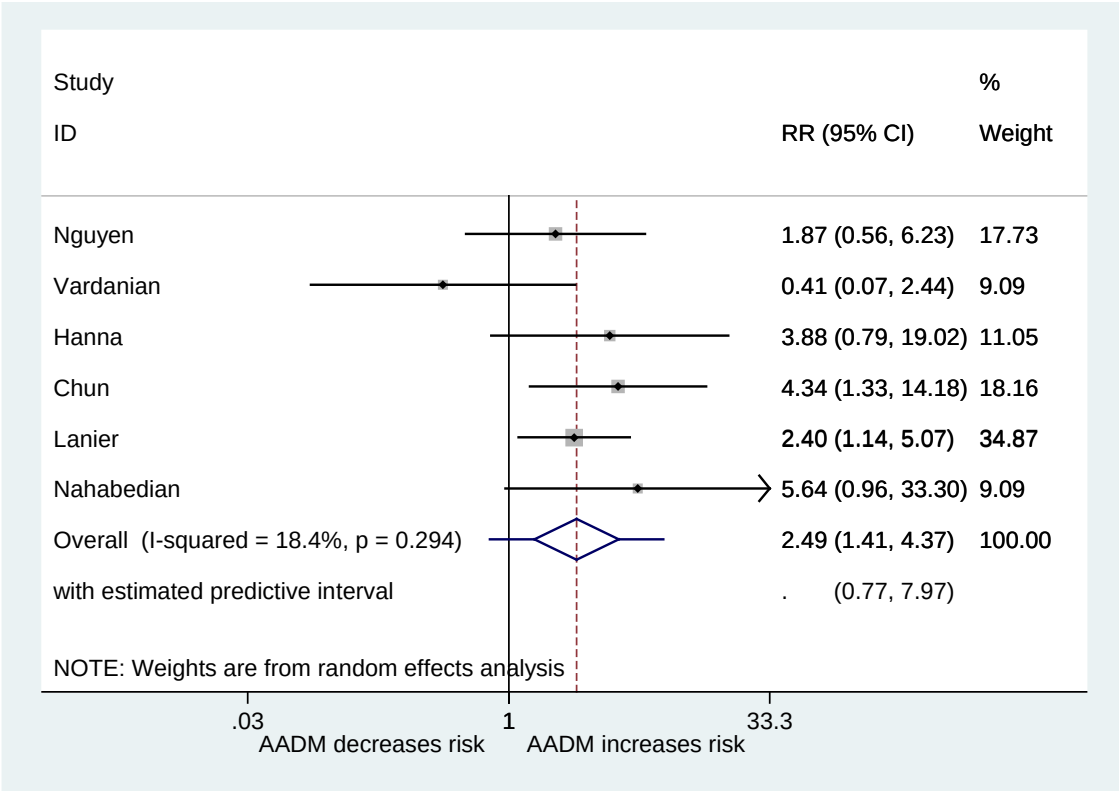
b)Exposure with implant loss/ explantation



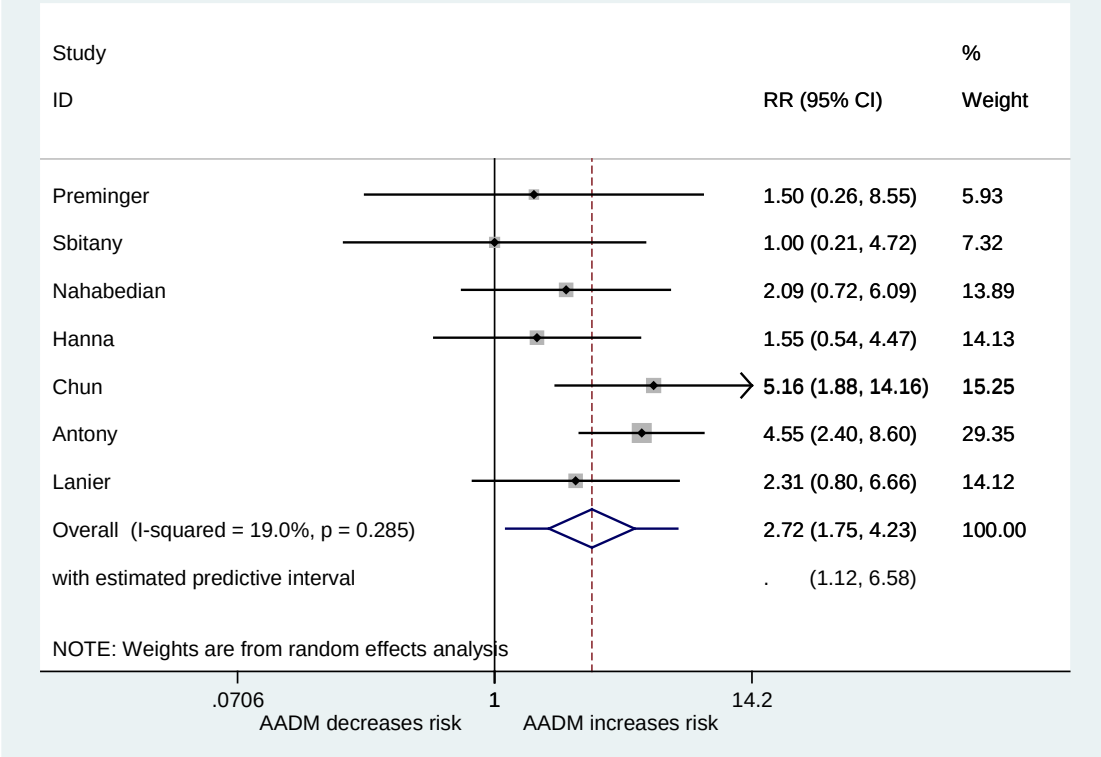
c)Major infection (leading to implant loss)



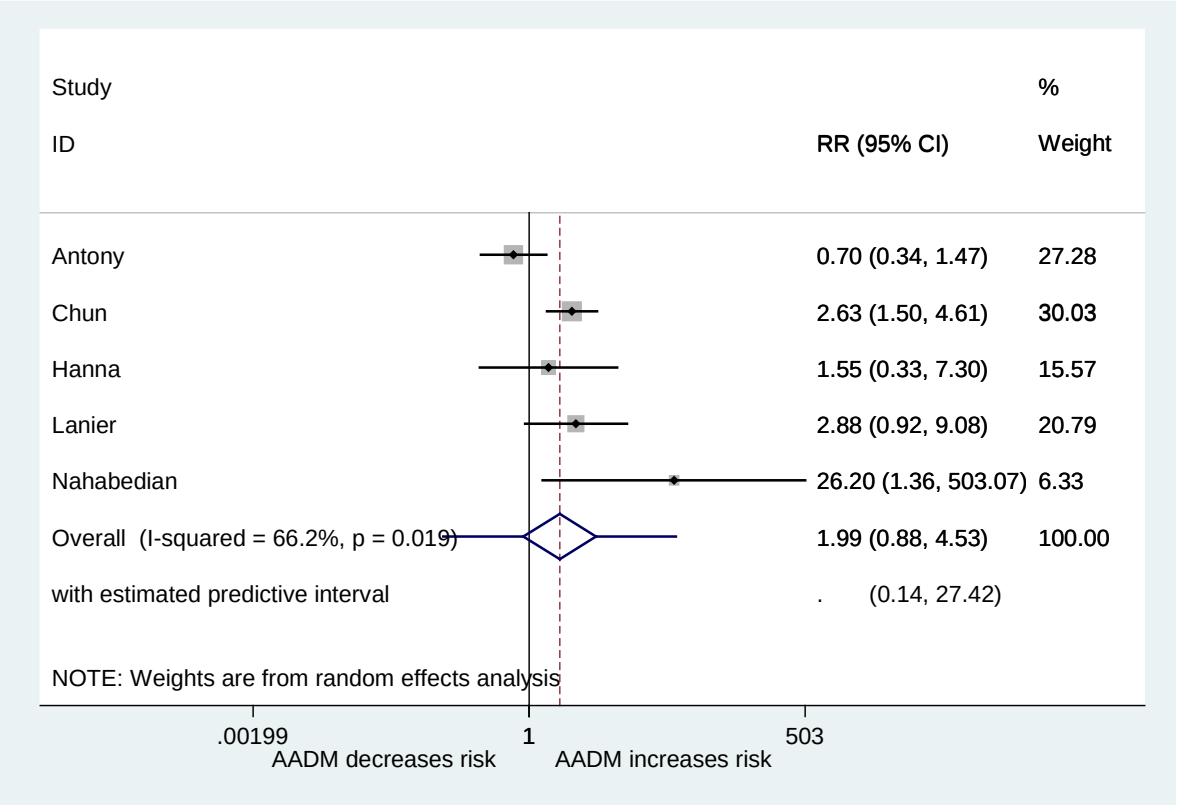
d)Minor infection (not leading to implant loss)



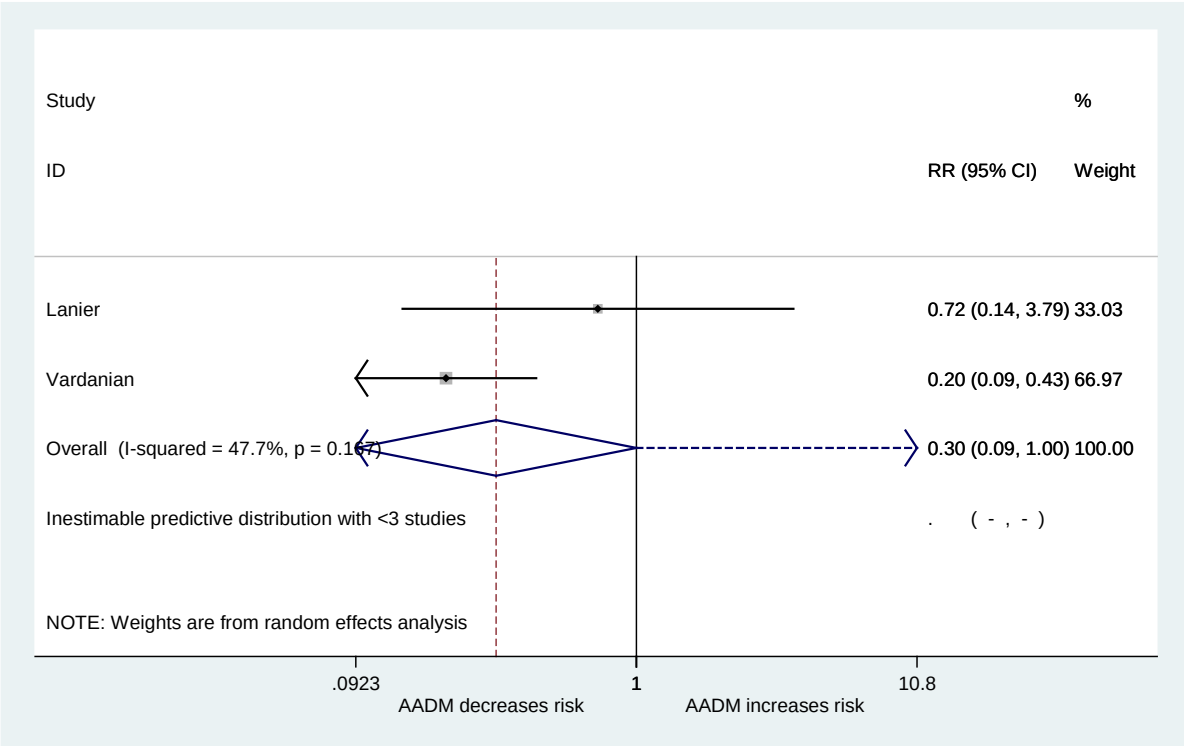
e)Seroma



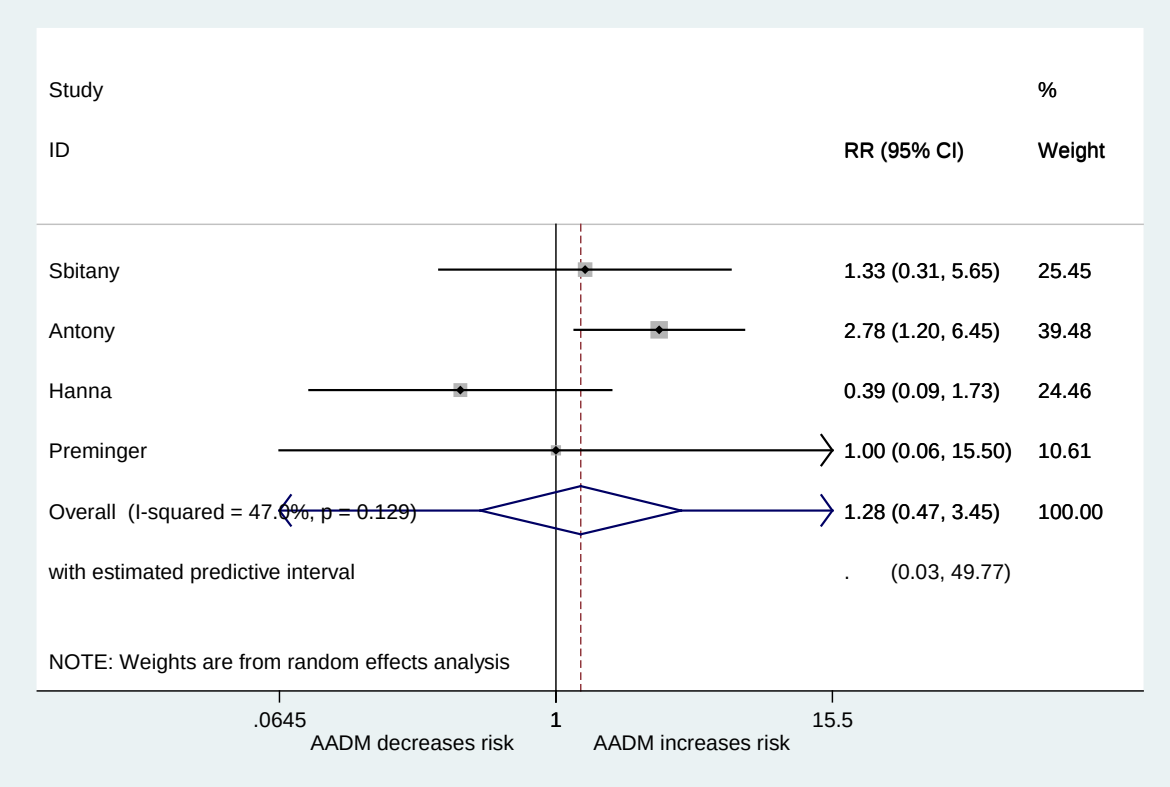
f)Partial flap/skin necrosis



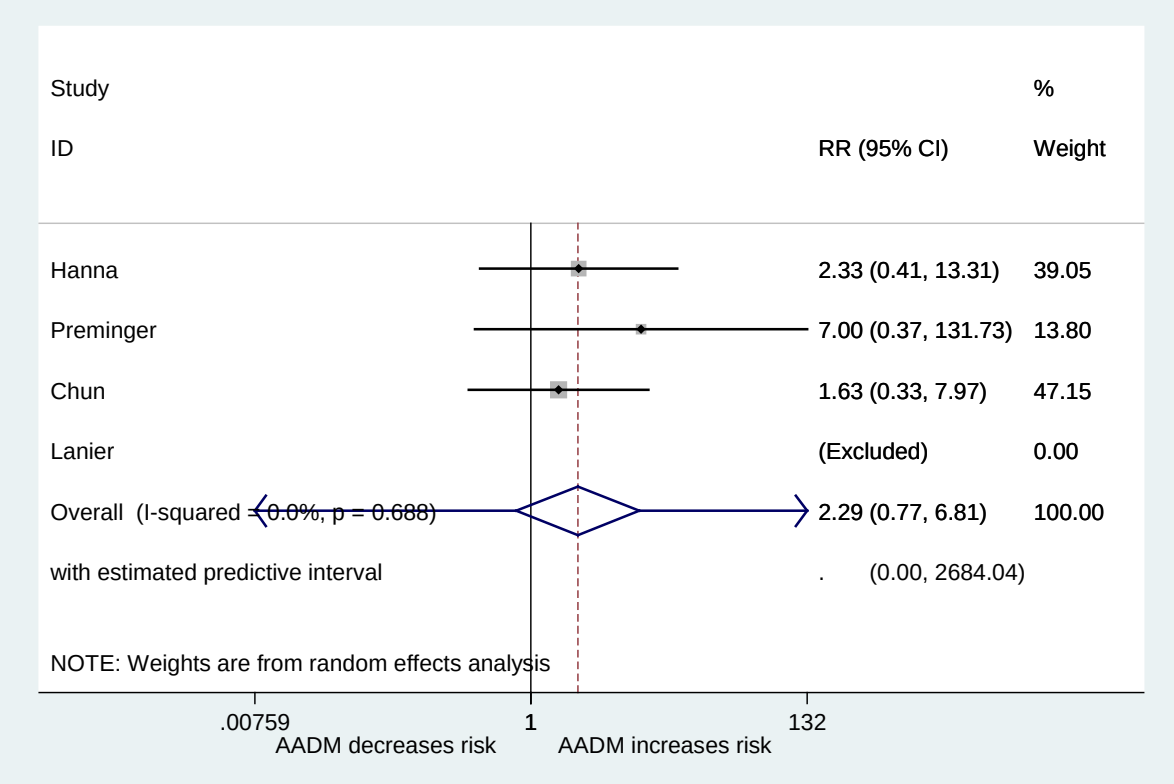
g)Capsular contracture



h)Cellulitis



i)Hematoma



APPENDIX 1

Assessment of Bias (Adapted from Downs and Black Checklist(10))

The questions can be answered with: Yes, No, Not reported, or Unclear

1. *Were the patients in different intervention groups (trials and cohort studies) recruited from the same population and over the same period of time?*

2. *Were the exposed and unexposed groups comparable in terms of the distribution of confounding variables?*

For example, patients for all comparison groups should be selected from the same hospital. Important confounding variables: age (mean difference of 5 years), BMI (mean difference of 5 kg/m^2), smoking, diabetes, radiation therapy [outside range 0.8-1.25 for risk ratios].

3. *Was an attempt made to blind those measuring the main outcomes of the intervention?*

4. *Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?*

This question should be answered no if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses.

5. *In the event of a difference in follow-up between the two groups, do the analyses adjust for different lengths of follow-up of patients?*

If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.

6. *Was there industry sponsorship, industry authorship (employment of an author by industry), contract research, receipt by authors of substantial personal financial benefit search, or equity interest to constitute conflict of interest?*

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