Peer Review File

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Reviewer A

Comment 1: study was done and impressed with the Low seroma rate and inclusion patients with smoker still low complications. Too early to comment on capsular contracture.

Reply 1: We thank the Reviewer for their comment. We agree on the fact that a median follow-up of 10 months is too short to drive firm conclusions on capsular contracture formation. Nevertheless, literature data show evidence of capsular contracture as early as 9.6 months of mean follow-up (Urquia et al., 2020). Fifteen patients in our cohort had a follow-up longer than 1 year and 3 patients longer than 2 years, and none of them developed capsular contracture. Hence, at least for 27% of patient, capsular contracture did not occur on the medium term. In addition, it must be considered that 20% of breasts underwent radiotherapy, a known risk factor for early onset of capsular contracture. Such complication was not observed in irradiated patients.

Changes in the text: We added information on the number of patients with follow-up longer than 1 year to better clarify the consideration on capsular contracture. Please see Page 10, lines 175-177.

Urquia LN, Hart AM, Liu DZ, et al. Surgical outcomes in pre-pectoral breast reconstruction. Plast Reconstr Surg Glob Open. 2020;8:e2744.

Comment 2: Did you do any lipofilling before changing to implant if any document.

Reply 2: We thank the Reviewer for their question. We performed lipofilling in 10.9% of patients. Fat grafting can be required in up to 20% of patients (depending on the patient's BMI, the ADM/mesh used, etc.) when DTI pre-pectoral reconstruction is performed (Masià et al., 2020; Scarabosio et al., 2023; Casella et al., 2019; Bernini et al., 2015). With two-stage pre-pectoral reconstruction there is the possibility to perform fat grafting at the time of tissue expander-implant exchange. This represents an advantage for the patient as she can avoid multiple interventions after she has healed.

Changes in the text: This detail was specified. Please see Page 9, lines 156, 157.

Masià J; iBAG Working Group. The largest multicentre data collection on prepectoral breast reconstruction: The iBAG study. J Surg Oncol. 2020 Oct;122(5):848-860. doi: 10.1002/jso.26073. Epub 2020 Aug 12. PMID: 32786089; PMCID: PMC7540676.

Scarabosio A, Contessi Negrini F, Pisano G, Beorchia Y, Castriotta L, De Francesco F, Riccio M, Parodi PC, Zingaretti N. Prepectoral Direct-To-Implant One-Stage Reconstruction With ADMs: Safety and Outcome in "Thin Patients". Clin Breast Cancer. 2023 Dec;23(8):e507-e514. doi: 10.1016/j.clbc.2023.08.007. Epub 2023 Aug 25. PMID: 37735018.

Casella D, Di Taranto G, Marcasciano M, Lo Torto F, Barellini L, Sordi S, Gaggelli I,

Roncella M, Calabrese C, Ribuffo D. Subcutaneous expanders and synthetic mesh for breast reconstruction: Long-term and patient-reported BREAST-Q outcomes of a single-center prospective study. J Plast Reconstr Aesthet Surg. 2019 May;72(5):805-812. doi: 10.1016/j.bjps.2018.12.018. Epub 2018 Dec 16. PMID: 30639155.
Bernini M, Calabrese C, Cecconi L, Santi C, Gjondedaj U, Roselli J, Nori J, Fausto A, Orzalesi L, Casella D. Subcutaneous Direct-to-Implant Breast Reconstruction: Surgical, Functional, and Aesthetic Results after Long-Term Follow-Up. Plast Reconstr Surg Glob Open. 2016 Jan 7;3(12):e574. doi: 10.1097/GOX.0000000000000533. PMID: 26893999; PMCID: PMC4727683.

Reviewer B

Comment 1: Although the paper is well-written, I do not find any novelty in the paper.

Reply 1: We thank the Reviewer for their comment. We agree on the fact that pre-pectoral positioning of a tissue expander wrapped with ADM does not represent a breakthrough in the breast reconstruction field. Yet, it must be recognized that, similar to what we see with ADM-assisted pre-pectoral breast reconstruction with definitive implants, performing the same technique using different ADMs (of different animal origin, meshed, fenestrated, with continuous surface, etc) or various degree of implant coverage (complete or partial) leads to non-homogeneous clinical results. Clinical research is proving that all ADMs are not equal. In Europe Braxon Fast is one of the most used ADMs. It is the only one specifically designed for breast reconstruction and that allows complete implant coverage. So far, there are no reports of complete tissue expander coverage with ADM in pre-pectoral position, as the published articles report incomplete wrap or the use of fenestrated ADMs which leave the implant exposed. In fact, covering an implant with rectangular or ovoidal ADM is possible, nevertheless, those shapes always leave big or small parts of the implant exposed. In addition, most of the biological matrices used are meshed or fenestrated, therefore the implant is not covered by the ADM on the spot of the fenestration. These ADMs force the operator to tailor them every time they are used, while Braxon Fast presents a pre-shaped design with a three-dimensional dome-shaped anterior part that allows for the easy allocation of the convexity of the implant. Other characteristics that differentiate Braxon Fast from other biological devices are the pig origin (the others are of human and bovine origin), and the attested adipogenic stimulation capacity, which makes it able to boost a more natural tissue regeneration. Therefore, the novelty in our work consists in showcasing for the first time the results of two-stage pre-pectoral breast reconstruction with a biological device which stands out for many aspects and that has never been tested in dynamic conditions, that is, tissue expansion. We also showed that expansion is possible even when a non-fenestrated ADM is used, this type of ADM usually considered not ideal because of poor extensibility.

Changes in the text: The text has been modified adding a few lines on the novelty (please see Page 11, lines 192-198).

Reviewer C

Reasonable paper with discussion points

Comment 1: Too fixed on material

Reply 1: We thank the Reviewer for their consideration. We have focused our attention on the material for various reasons. Clinical research is proving that all ADMs are not equal. Similar to what we see with ADM-assisted pre-pectoral breast reconstruction with definitive implants, performing the same technique using different ADMs (of diverse animal origin, meshed, fenestrated, with continuous surface, etc.) or various degree of implant coverage (complete or partial) leads to non-homogeneous clinical results. In Europe Braxon Fast is one of the most used ADMs. It is the only one specifically designed for breast reconstruction and that allows complete implant coverage. To our knowledge, there are no reports of complete tissue expander coverage with ADM in pre-pectoral position, as the published articles report incomplete wrap or the use of fenestrated ADMs which leave the implant exposed. In fact, covering an implant with rectangular or ovoidal ADM is possible, nevertheless, those shapes always leave big or small parts of the implant exposed. In addition, most of the biological matrices used are meshed or fenestrated, therefore the implant is not covered by the ADM on the spot of the fenestration. These ADMs force the operator to tailor them every time they are used, while Braxon Fast presents a pre-shaped design with a three-dimensional dome-shaped anterior part that allows for the easy allocation of the convexity of the implant. Other characteristics that differentiate Braxon Fast from other biological devices are the pig origin (the others are of human and bovine origin), and the attested adipogenic stimulation capacity, which makes it able to boost a more natural tissue regeneration. We showcased for the first time the results of two-stage pre-pectoral breast reconstruction with a biological device never tested in dynamic conditions, that is, tissue expansion. Our aim was also to show that expansion is possible even when a non-fenestrated ADM is used, usually considered not ideal because of their poor extensibility, and that the material used can still stimulate tissue regeneration. Ultimately, thanks, to this surgical procedure, when done as we described the pre-pectoral technique can be safely offered to a wider audience, allowing more cancer patients to benefit from pectoralis major muscle sparing.

Changes in the text: The text has been modified clarifying why our attention was focused on the material (please see Page 11, lines 192-198).

Comment 2: Ads little to literature

Reply 2: We thank the Reviewer for their comment. As all ADMs are not equal, we consider of paramount importance to investigate the clinical potential of such

devices in all possible applications, always keeping as main goal patient's wellbeing. As regards Braxon Fast ADM specifically, data on its application with tissue expanders implanted in pre-pectoral position were lacking. Our work may not be groundbreaking, though we see its implications on the clinical practice: by exploring how a given device works in a specific technique us surgeons gain a more comprehensive knowledge on our tools so that, ultimately, we can offer the most appropriate reconstructive technique, tailored on each patient's characteristics, and needs. In our view this work adds another tile in ADM in breast reconstruction literature as Braxon Fast stands out for many aspects: the pig origin (the others are of human and bovine origin), the complete implant surface for a homogeneous tissue regeneration, the attested adipogenic stimulation capacity, which boosts a more natural tissue regeneration, the three-dimensional dome-shaped design for an easy and standardized implant wrapping. Braxon Fast was born for DTI pre-pectoral breast reconstruction. Now, thanks to this work, it is proved that its application can be extended to two-stage pre-pectoral breast reconstruction.
Changes in the text: We have modified the text with a comment (please see Page 14, lines 267-270).

Good bibliography

Reviewer D

Comment 1: Interesting manuscript discussing the benefits of pre-pectoral breast reconstruction, especially in this age where we see a resurgence in the method. This has, however, been extensively presented and written about in the literature. The novelty in your manuscript is more the ADM used (porcine based) rather than the method of wrapping, which has been long done.

Reply 1: We thank the Reviewer for their comment. We agree on the fact that the ADM used represents the novelty of our work. From our point of view, however, the animal source is just one half of such novelty. In fact, Braxon Fast is the only ADM specifically designed for pre-pectoral breast reconstruction with a continuous surface and with a pre-shaped 3D conformation that allows complete wrap of the ADM without forcing the operator to cut and sew the material so to create *ad hoc* shapes. Covering an implant with rectangular or ovoidal ADM is possible, nevertheless, those shapes always leave big or small parts of the implant exposed. In addition, most of the biological matrices used are meshed or fenestrated, therefore the implant is not covered by the ADM on the spot of the fenestration. Lastly, Braxon Fast stands out also for the three-dimensional dome-shaped design for an easy and standardized implant wrapping, and for the attested adipogenic stimulation capacity which boosts a more natural tissue regeneration. In light of this, we consider our work to be the first one reporting the complete wrap of a tissue expander placed in the pre-pectoral space, and, additionally, with a porcine-based device presenting a 3D dome shape.

Changes in the text: The text has been modified adding a few lines on the novelty (please see Page 11, lines 192-198).

Reviewer E

The authors are to be complimented for this paper on "Pre-pectoral breast reconstruction with tissue expander entirely covered by acellular dermal matrix feasibility, safety and histological features resulting from the first 64 procedures".

However, I would suggest the following revisions

Comment 1: Please specify why a two-step procedure has been chosen for this group of patients. From the inclusion criteria, it is unclear if a DTI procedure has been offered, if the patients have been directly proposed a TE reconstruction for the purpose of this study (which is unlikely, being this a retrospective study and not a trial) if TE reconstruction is the only method available in the institution. Please specify.

Reply 1: We thank the Reviewer for their suggestion. At our institution both DTI and two-stage pre-pectoral reconstructions are offered. The two-step procedure is offered to patients who would benefit from the sparing of the pectoralis major muscle but who are not good candidates for direct-to-implant reconstructions because of obesity, previous radiotherapy treatment, hypertension, neo-adjuvant chemotherapy, and undergoing a skin-sparing procedure (because of nipple-areola complex removal). In our work we included these patients, plus those who had small breasts and were wishing for a larger cup. We maintained the pre-pectoral philosophy so to offer the functional and aesthetic advantages that such technique possesses.

Changes in the text: We have modified the text specifying the inclusion criteria. Please see Pages 7-8, lines 112-118.

Comment 2: Could you rewrite your inclusion criteria in view of the previous comment? Also, is the use of another ADM the only exclusion criterion? There is no mention of TNM status, neoadjuvant or adjuvant treatments, or patient age. Please clarify.

Please elaborate and include these characteristics

Reply 2: We thank the Reviewer for their suggestion and questions. The inclusion criteria have been rewritten in the view of the previous comment.

At our institution Braxon Fast is the only ADM used. Until recently, a synthetic mesh was also employed (now dismissed) and patients with such device were not included in the analysis.

Neoadjuvant or adjuvant treatments and patient age are reported in Table 1. The TNM status is now specified in the text.

Changes in the text: We have modified the text specifying the inclusion criteria, including the TNM status (please see Page Pages 7-8, lines 112-118). Patient age,

and neoadjuvant or adjuvant treatments are reported in Table 1.

Comment 3: Two-stage reconstruction is not cost-effective and also has a negative impact on patients' QoL (quality of life). These aspects should be evaluated in the paper. Please integrate and add proper references.

Reply 3: We thank the Reviewer for their comment. While we agree on the least cost-effectiveness of two-stage compared to one-stage pre-pectoral reconstruction, for some patients such procedure represents the opportunity to save the pectoralis major muscle, even if this means that some advantages of the one-stage procedure must be sacrificed. In fact, we consider two-stage pre-pectoral reconstruction as the best alternative to submuscular reconstruction, and not a downgrade of the pre-pectoral procedure. Cost-effective analyses consider multiple practical aspects; however, they never consider the economic cost of the pectoralis muscle and of its functional loss with all the relative fallouts on patients' QoL. With this surgical procedure we have maintained the pre-pectoral philosophy so to offer the functional and aesthetic advantages that such technique possesses to those patients who would have had complications if they had undergone the pre-pectoral DTI technique. In the best-case scenario, DTI in non-suitable patients bounds them to a long medication journey with poor QoL and an economical burden. In the worst, patients would face reconstructive failure, which also has a cost. For specific patients we thought it appropriate to avoid a therapeutic path which, if complicated, would be worse.

Changes in the text: We have modified the text as suggested (please see Pages 14-15, lines 270-276).

Comment 4: Please do a grammar check to improve fluency and to check for possible mistakes.

Reply 4: We thank the Reviewer for their comment. In accordance with Reviewer suggestions, we have undertaken a review of the manuscript. A rigorous grammar check has been conducted to address these concerns and enhance the overall clarity and coherence of the text.

Changes in the text: Involving the entire text.

Comment 5: Please clarify how you evaluated the effectiveness of the technique since you only had one group of patients. As highlighted before, it is not cost-effective, and patient satisfaction has not been evaluated (BREAST-Q).

Reply 5: We thank the Reviewer for their feedback. While we acknowledge the importance of BREAST-Q analysis and case control studies, we believe that these components fall outside the scope of our current investigation. Our emphasis was on providing an assessment of the safety and efficacy of our novel approach to two-stage pre-pectoral reconstruction technique. At the same time, we aimed at contributing to the understanding of the regenerative capacity of a porcine dermal matrix specifically designed and pre-shaped for the pre-pectoral procedure

through an essential but informative histological investigation on the capsules around the implant.
The effectiveness of our technique was evaluated from the clinical point of view, considering complication rates. The comparison of our data with literature findings, specifically considering Braxon and Braxon Fast publications, supports our claim that the complications associated with our procedure are comparable to established methods, thereby reinforcing the efficacy of our approach. We agree on the fact that BREAST-Q analyses ultimately provide a comprehensive insight into the efficacy of the procedure. It is in our plans to follow-up this work with more data and patients' feedback on a longer term, at the end of the reconstructive course (after the second stage).
Changes in the text: We have modified the manuscript and added a consideration on this matter in the Discussion section (please see Page 13, lines 231-232).

Comment 6: Can you provide the reference in which the Braxon Fast ADM promotes subcutaneous tissue regeneration? To my knowledge there is none, please rephrase. You might have confused subcutaneous tissue with the capsule.
Reply 6: We are thankful to the Reviewer for their question. Braxon Fast is the technological upgrade of Braxon ADM. The devices share the scientific rationale, the biological characteristics, and the literature, as the only difference is the presence of the 3D dome shape on Braxon Fast. The capsule that forms when Braxon/Braxon Fast is used does not present with the same biological characteristics of the capsule formed around naked synthetic implants or synthetic meshes. Literature data report that, besides the thin layer of synovial metaplasia, there are no signs of fibrosis or inflammation, the collagen fibers are oriented following natural ECM structure and there is no excess of myofibroblasts. Cells repopulate the matrix and neovascularization occurs, indicating matrix tissue integration and regeneration (Iqbal et al., 2016; Onesti et al., 2017; Caputo et al., 2015). In addition, only these devices showed adipogenic stimulation capacity *in vitro* and *in vivo* (Quintero-Sierra et al., 2021). With Braxon Fast ADM subcutaneous tissue regeneration takes place because, by avoiding the foreign body response triggered by the presence of the synthetic implant, the inflammation-mediated collagen deposition does not occur (Cramer and Badylak, 2020).
Changes in the text: The text has been modified adding a few words and relative bibliography in the Introduction section (please see Page 6, line 80-81 and references 6-8).
Iqbal FM, Bhatnagar A, Vidya R. Host Integration of an Acellular Dermal Matrix: Braxon Mesh in Breast Reconstruction. Clin Breast Cancer. 2016 Dec;16(6):e209-e211. doi: 10.1016/j.clbc.2016.06.009. Epub 2016 Jun 27. PMID: 27471076.
Onesti MG, Maruccia M, Di Taranto G, Albano A, Soda G, Ballesio L, Scuderi N. Clinical, histological, and ultrasound follow-up of breast reconstruction with one-stage muscle-sparing "wrap" technique: A single-center experience. J Plast

Reconstr Aesthet Surg. 2017 Nov;70(11):1527-1536. doi: 10.1016/j.bjps.2017.06.023. Epub 2017 Jun 29. PMID: 28736191.
Caputo GG, Franchini Z, Maritan M, Dalla Pozza E, Vigato E, Tedeschi U, Governa M. Daily serum collection after acellular dermal matrix-assisted breast reconstruction. Arch Plast Surg. 2015 May;42(3):321-6. doi: 10.5999/aps.2015.42.3.321. Epub 2015 May 14. PMID: 26015888; PMCID: PMC4439592.
Quintero Sierra LA, Busato A, Zingaretti N, Conti A, Biswas R, Governa M, Vigato E, Parodi PC, Bernardi P, Sbarbati A, Conti G. Tissue-Material Integration and Biostimulation Study of Collagen Acellular Matrices. Tissue Eng Regen Med. 2022 Jun;19(3):477-490. doi: 10.1007/s13770-021-00420-6. Epub 2022 Mar 4. PMID: 35244884; PMCID: PMC9130448.
Cramer MC, Badylak SF. Extracellular Matrix-Based Biomaterials and Their Influence Upon Cell Behavior. Ann Biomed Eng. 2020 Jul;48(7):2132-2153. doi: 10.1007/s10439-019-02408-9. Epub 2019 Nov 18. PMID: 31741227; PMCID: PMC7231673.

Comment 7: Could you provide a reference for the good medical practice standards you are referring to? Are you referring to national guidelines, in the literature? Please rephrase

Reply 7: We are thankful to the Reviewer for their questions. In our manuscript, when we refer to "good medical practice standards," we are drawing upon established guidelines and benchmarks present in the scientific literature. As an example, we have referred to Knight et al. which discuss the National Oncoplastic Guidelines for Best Practice and advocate for a target implant loss rate of less than 5% at 3 months post-operation. Compared to this benchmark, our implant loss and each of our reported complications individually falls below the specified 5% threshold, underscoring the alignment of our results with the principles of good clinical practice. Additionally, we have benchmarked our outcomes against the standards set by the 2019 international joint consensus guide for implant-based prepectoral reconstruction (Vidya et al., 2019): all our results not only meet but also fall within the desirable parameters outlined in this comprehensive guide. This comparison further supports the reliability of our findings.

Changes in the text: We have added the appropriate bibliography (please see Page 13, line 231).

Knight HJ, Musgrove JJ, Youssef MMG, Ferguson DJ, Olsen SB, Tillett RL. Significantly reducing implant loss rates in immediate implant-based breast reconstruction: A protocol and completed audit of quality assurance. J Plast Reconstr Aesthet Surg. 2020 Jun;73(6):1043-1049. doi: 10.1016/j.bjps.2019.12.005. Epub 2019 Dec 27. PMID: 32008945.
Vidya R, Berna G, Sbitany H, Nahabedian M, Becker H, Reitsamer R, Rancati A, Macmillan D, Cawthorn S. Prepectoral implant-based breast reconstruction: a joint consensus guide from UK, European and USA breast and plastic reconstructive surgeons. Ecancermedicalscience. 2019 May 7;13:927. doi:

10.3332/ecancer.2019.927. PMID: 31281424; PMCID: PMC6592711.

Comment 8: Please shorten the lengthy introduction, it can be easily halved.
Reply 8: We thank the Reviewer for their suggestion. The lenght of the Introduction was to better enable us to emphasize the scientific rationale and the novelty of our work. We are happy to reduce it as recommended.
Changes in the text: The Introduction section has been shortened (please see Pages 5-7, lines 72-106).

C**omment 9: 94-95 Please specify "first reconstruction with Braxon" if you wish or correct it with the appropriate reference (for your knowledge, hereby attached is a metanalysis about PPBR from which you might retrieve useful information which you can use throughout the paper**
"Tellarini A, Garutti L, Corno M, Tamborini F, Paganini F, Fasoli V, Di Giovanna D, Valdatta L. Immediate post-mastectomy pre-pectoral breast reconstruction with animal derived acellular dermal matrices: A systematic review. J Plast Reconstr Aesthet Surg. 2023 Nov;86:94-108. doi: 10.1016/j.bjps.2023.08.020. Epub 2023 Aug 24. PMID: 37716255")
Reply 9: We thank the Reviewer for their appropriate proposal and for the suggested paper. We have modified the text accordingly to provide more clarity. The appropriate reference is already present in the text (number 5).
Changes in the text: We have modified the text as advised (please see Page 6, lines 92-93).

Comment 10: Can you include the Ethic Committee approval number for the protocol of the study?
Reply 10: We thank the Reviewer for their question. The Ethic Committee approval number for the protocol of the study (NO: #16.069_AOUC) is already reported in the Ethical Statement paragraph.
Changes in the text: none.

Comment 11: Could you specify do you mean by comorbidity?
Reply 11: We thank the Reviewer for their question. According to the definition (as reported in the Merriam Webster Medical Dictionary: all the pathological conditions existing simultaneously with and usually independently of another medical condition) we have considered as comorbidity all those patient's pathologies present at the time of surgery, as they can influence the reconstructive outcome (and are therefore considered as risk factors).
Changes in the text: none.

Comment 12: Monocryl 3-0 takes longer to dissolve 90-120 days to be completely resorbed. Please remove the sentence.
Reply 12: We thank the Reviewer for their observation. The suture used is Vicryl Rapide, which takes 42 days to adsorb.

Changes in the text: The text was modified specifying the suture brand. Please see Page 9, lines 141, 142.

Comment 13: Statistical analysis is very weak. Please elaborate on the data with statistician support to provide scientific evidence for your paper.
Reply 13: We are thankful to the Reviewer for their consideration. As specified in the Materials and Methods section, data are presented as a descriptive analysis of demographical and surgical data, and complications. No univariate statistical analyses have been performed as no control group is present and no risk-factors-complication relations were envisioned, because of the small numerosity of our cohort.
Changes in the text: none.

Comment 14: Please avoid repetition of the data already summarised in the tables. Remove all unnecessary repetitions from the text.
Reply 14: We thank the Reviewer for their suggestion. Demographic data have been streamlined in the text.
Changes in the text: we modified the text accordingly and removed parts of the text in the Results section (please see Page 10, lines 164-168).

Comment 15: The three-month follow-up cannot be considered long-term. Please rephrase where necessary.
Reply 15: We are thankful to the Reviewer for their comment. We agree with the Reviewer that a three-month follow-up is not long-term. We checked the manuscript and confirmed that such thing is not stated anywhere. We have also changed "short-term" and "long-term" with "early" and "late", which are more appropriate for defining the timing of complication occurrence (before and after three months from surgery, respectively).
Changes in the text: We have modified the text removing "short-term" and "long-term" and substituting with "early" and "late" when complications are discussed. Please see Page 8, line 126,127; Page 10, lines 169 and 172; Page 13, line 233.

Comment 16: BREAST-Q was not performed, in view of that please remove subjective opinion from the paper (Line 186 187).
Reply 16: We thank the Reviewer for their suggestion. We have modified the text accordingly.
Changes in the text: The text was modified rephrasing the sentence (please see Page 11, line 184).

Comment 17: The discussion is lengthy and not to the point, please rewrite, and shorten it. When needed, add proper references.
Reply 17: We thank the Reviewer for their suggestion. The Discussion section has been revised making it more concise on the novelty of the work (biological material used, its scientific rationale, the 3D shape, and the full expander coverage)

and shortened. New references have been added.
Changes in the text: We have modified the text as advised and shortened the Discussion section (please see Pages 11-15, lines 188-280). New references added with number 26, 27, 39, 40, 41,52.

Comment 18: Please rephrase Line 233 234, it seems a sentence with no scientific value in this context.
Reply 18: We thank the Reviewer for their comment. Our aim was to highlight that literature data on this topic are heterogeneous because of the heterogeneous tissue expander's surface coverage. Different ADMs not designed for complete implant wrap do not allow for a standardize method of implant wrapping, thus forcing the operators to create their own. Not only this means that for each ADM there will be a different amount of uncovered implant surface, but also that centre-to-centre variability is a reality. It is well known that leaving the synthetic material (that is, the implant) in contact with the subcutaneous tissue promotes inflammation that leads to complications: seroma *in primis*, and capsular formation (and, eventually, capsular contracture). Because of this variability, data on pre-pectoral breast reconstruction with ADM-enveloped tissue expanders cannot be generalized.
Changes in the text: We have modified the text rephrasing that sentence (please see Page 13, lines 227-228).

Comment 19: The histopathology should be explored more, to add scientific value to your paper.
Reply 19: We thank the Reviewer for their suggestion. We would like to specify that extensive histopathological analyses are beyond the scope of our work. While acknowledging the added scientific value those analyses would bring, unfortunately, at this moment is not possible for us to perform additional histopathological investigations. It is in our plans give a pivotal role to those investigations in our next publication as a follow-up of this work, performing qualitative and quantitative analyses (by means of immunofluorescence) on collagen fibers orientation in the long term.
Changes in the text: We modified the manuscript and added a consideration on this matter in the limitation paragraph in the Discussion section (please see Page 14, lines 260-262).

Reviewer F
The authors present a small retrospective series of pre-pectoral two-stage breast reconstruction with ADM coverage.

Comment 1: There is a vast body of literature with large sample sizes and comparative data on two-stage pre-pectoral breast reconstruction with and without ADM. This includes complete and partial wrap techniques. What

aspects of the study do the authors feel is novel compared to the prior literature?

Reply 1: We thank the Reviewer for their comment. We agree on the fact that pre-pectoral positioning of a tissue expander wrapped with ADM does not represent a breakthrough in the breast reconstruction field, and that there are published papers with larger sample sizes and comparative data. Yet, it must be recognized that, similar to what we see with ADM-assisted pre-pectoral breast reconstruction with definitive implants, performing the same technique using different ADMs (of different animal origin, meshed, fenestrated, with continuous surface, etc.) or various degree of implant coverage (complete or partial) leads to non-homogeneous clinical results. Clinical research is proving that all ADMs are not equal. In Europe Braxon Fast is one of the most used ADMs. It is the only one specifically designed for breast reconstruction and that allows complete implant coverage. To our knowledge, there are no reports of complete tissue expander coverage with ADM in pre-pectoral position (one report with synthetic mesh – Bernini et al., 2022), as the published articles report incomplete wrap or the use of fenestrated ADMs which leave the implant exposed. In fact, covering an implant with rectangular or ovoidal ADM is possible, nevertheless, those shapes always leave big or small parts of the implant exposed. In addition, most of the biological matrices used are meshed or fenestrated, therefore the implant is not covered by the ADM on the spot of the fenestration. These ADMs force the operator to tailor them every time they are used, while Braxon Fast presents a pre-shaped design with a three-dimensional dome-shaped anterior part that allows for the easy allocation of the convexity of the implant. Other characteristics that differentiate Braxon Fast from other biological devices are the pig origin (the others are of human and bovine origin), and the attested adipogenic stimulation capacity, which boosts a more natural tissue regeneration. The novelty in our work consists in showcasing for the first time the results of two-stage pre-pectoral breast reconstruction with a biological device never tested in dynamic conditions, that is, tissue expansion. We also showed that expansion is possible even when a non-fenestrated ADM is used, usually considered not ideal because of their poor extensibility, and that the material used can still stimulate tissue regeneration.

Changes in the text: The text has been modified adding a few lines on the novelty (please see Page 11, lineS 192-198).

Comment 2: The use of the term "temporary implant" rather than tissue expander is confusing.

Reply 2: We thank the Reviewer for their comment. The term "temporary implant" has been substituted with "tissue expander".

Changes in the text: We modified the text accordingly (Please see Page 3, line 49; Page 4, lines 56 and 59, Page 7, lines 103.