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# Pre-pectoral Breast Reconstruction Does Not Affect Early Immunological Response: A BIAL 2.20 Study Subanalysis

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**Abstract.** *Background/aim: Reduction of postoperative stress is a modern tenet in surgical oncology with the aim of reducing early postoperative lymphopenia. Our prospective study evaluated post-operative immune response at baseline and postoperative day (POD) 1 and 2 after direct-to-implant pre-pectoral (PP) breast reconstruction with titanium-coated polypropylene mesh versus subpectoral (SP) breast reconstruction. Patients and Methods: Between January and December 2020, 37 patients were randomized between PP (n=17) or SP (n=16) reconstruction. Baseline and operative data were analyzed. Postoperative pain assessment using numeric pain rating scale (NPRS), and a full blood count with lymphocyte subsets were collected before surgery, and on POD1 and POD2. Data were evaluated by two-way analysis of variance test. Results: Baseline data did not demonstrate any statistical difference. Inter-group analysis did not provide any statistically significant difference in leukocytes, total lymphocytes, and lymphocytes subsets among SP and PP reconstruction groups (p>0.05). However, compared to specificity, the PP group experienced shorter operative time, with a mean difference 30.19 min, lower blood loss (p=0.017), lower rate of postoperative anemia (p=0.039), and a more favorable profile in inter-group pain analysis (p<0.001). Conclusion: PP reconstruction with titanium-coated polypropylene mesh does not increase immunological impairment in the early postoperative period when compared with SP reconstruction and provides lower postoperative pain, reduction of operative time, and lower rate of postoperative anemia.*

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*Key Words:* Breast neoplasm, immunosuppression, breast implants, surgical mesh, anemia, pain, postoperative, pre-pectoral breast reconstruction, titanium-coated polypropylene mesh.

Breast cancer represents the most common neoplasia in the world, affecting 2.1 million individuals per year globally (1). Notwithstanding the popularity of conservative techniques to reduce surgical impact of the primary tumor (2-5) and axillary disease (6-8), mastectomy followed by breast reconstruction is still required in certain clinical contexts (9). Modern reconstruction in breast cancer has shifted from oncological radicality and simple maintenance of body image and appearance towards enhancement of aesthetics in selected patients (10, 11). A single-stage direct-to-implant (DTI) alloplastic breast implant reconstruction represents the most prevalent technique in the clinical practice (12).

Besides traditional subpectoral (SP) reconstruction, pre-pectoral (PP) reconstruction has gained popularity during recent years owing to the introduction of acellular dermal matrix (ADM) and titanium-coated poly propylene mesh (TCPM) (13). SP reconstruction, in fact, requires elevation of the *pectoralis major* and *serratus anterior* muscles to provide prothesis coverage, while in the PP reconstruction, the prothesis is located anterior to the muscle, surrounded by ADM or TCPM (14).

When compared with SP reconstruction, PP reconstruction is associated with similar complication rates, but lower postoperative pain, lower opioid consumption (15) and faster postoperative recovery (16). Reduction of postoperative stress is the mainstay of modern surgical oncology (17). Emerging evidence demonstrates how different anesthetic regimens might eventually determine early postoperative lymphopenia (2, 18-20), a novel risk factor for early postoperative complications (21), and long-term control over oncological disease (22).

Despite promising outcomes regarding postoperative recovery and esthetic results (15, 16), little is known regarding the immunological impact of PP reconstruction. In

our recent study, we demonstrated that the surface of different textured breast implants may have promoted postoperative lymphocyte impairment through periprosthetic recruitment of lymphocytes (23). Consequently, we postulated that use of TCPM may have an impact on postoperative lymphocyte response. In view of this, the aim of the present study was to underline the role of PP breast reconstruction with TCPM in early postoperative response.

## Patients and Methods

*Study design and patient selection*. A single-center, prospective observational trial (SP reconstruction group versus PP reconstruction group) (Figure 1) was designed. The local Institutional Review Board approved this analysis within the larger BIAL2.20 study [registration number of Comitato Etico Indipendente (CEI) no. 15/20]. BIAL2.20 was funded by the Italian Ministry of Health (Fund no. E84E19002740006). The sample size was calculated according to data obtained from already published results of the BIAL 2.20 study (20). The primary endpoint was defined as a 10% difference between the groups in the absolute number of T-helper cells on postoperative day 2 (POD2). After having set an alpha error at 0.05 with a power analysis of 80%, the sample size was established at 32 patients, 16 for each group.

The primary inclusion criteria were diagnosis of non-metastatic breast cancer treated with mastectomy plus DTI PP breast reconstruction. In our clinical practice, PP reconstruction is offered in non-smoker patients with preoperative pinch test ≥2 cm, no history of connective tissue disease, and body mass index between 18 and 30 kg/m$^2$. Other inclusion criteria for the study were age between 18 and 70 years, female gender, and no usage of anti-inflammatory or β-agonists drugs during the 2 months prior to the operation. Moreover, patients who underwent a mastectomy following breast-conserving treatment for breast cancer or chest wall radiotherapy were excluded (3, 5). Due to the nature of the study and the different primary endpoint regarding the T-helper subset on POD2, the observational period was terminated at 30 days from the surgical procedure. After enrollment, patients were randomized between the two different procedures (DTI SP *vs*. DTI PP reconstruction) leaving all the physicians involved in preoperative and postoperative care unaware of the surgical procedure (double-blind study). The operating plastic surgeon was informed of the surgical technique immediately prior to surgical reconstruction in the theatre.

According to the criteria above, the BIAL2.20 study was initiated in January 2020 and terminated in December 2020.

*Preoperative assessment*. Before recruitment, all patients meeting the inclusion criteria for DTI PP breast reconstruction underwent a pre-operative plastic surgery consultation. During the visit, patients were counselled regarding each type of surgical approach (PP *vs*. SP) and signed a specific written-informed consent for participation in the study. After consultation, the patient's tailored prothesis was chosen by the plastic surgeon for both procedures (DTI PP and DTI SP).

*Venous blood sampling times*. At 7.30 a.m., prior to surgery, a venous blood sample was taken from the antecubital peripheral vein of the patient's arm. On POD1 and POD2, samples were collected at the same time. This specific point in time was selected in accordance with previous studies from the literature using this timeframe to evaluate lymphocyte response in different surgical procedures (2, 20, 24).

Complete blood count, total leukocyte, total lymphocyte, total T-lymphocyte, T-helper lymphocyte, cytotoxic T-lymphocyte, natural killer (NK) cell, and B- lymphocyte data were collected in absolute numbers and percentages. Samples were processed using a cell counter (Coulter Beckmann, MedLab, Cupertino, CA, USA). A BD FACS Calibur (BD Biosciences, Franklin Lakes, NJ, USA) instrument was employed for three-color cytometry (25). Lymphocyte subsets were obtained by incubating blood samples for 30 min with monoclonal antibodies at 4˚C. The percentage of the different subsets was calculated by differential gating after three-color cytometry.

*Surgical techniques*. All patients were placed in a supine decubitus position and underwent a nipple-sparing mastectomy. After a lateral radial S-italic incision, a retro areolar nipple biopsy was performed with frozen section to exclude residual disease in the nipple margin, and subsequently, a subcutaneous mastectomy was performed. When the nipple margin was involved by neoplasia according to the intraoperative assessment, patients were excluded from the analysis. Following the removal of the breast tissue, patients underwent reconstruction according to randomization (SP *vs*. PP). The plastic surgeon was unaware of the breast reconstruction strategy for the entire period of the study.

For the SP reconstruction, after elevation of the *pectoralis major* and *serratus anterior* muscles, a smooth round breast implant (Cohesive I®; Mentor, Santa Barbara, CA, USA) was placed.

For the PP reconstruction, immediate breast reconstruction was performed using a TCPM-wrapped definitive implant, TiLoop® Bra pocket (pfm medical, Cologne, Germany). The TCPM was first secured with resorbable sutures to create the pocket for the smooth round breast implant (Cohesive I®) in a separate surgical room during mastectomy to maintain study blindness.

Following *ex vivo* preparation, a TCPM-wrapped implant was placed in the PP position. Medial and lateral borders of the TCPM were secured with interrupted resorbable sutures. Subsequently, one or more suction drainages were placed according to the surgeon's choice, and were removed when the serous fluid loss was less than 30 ml/24 h. Contralateral symmetrization techniques without breast implant, mastopexy or contralateral mirroring were included in the study but procedures including contralateral breast implants were excluded. In order to minimize potential bias associated with the effect of anesthetic regimen on the early immunological response, all procedures were carried out with endovascular administration of propofol, and supraglottic devices were used for airway management (2, 24). Whenever the anesthetic regimen changed during the procedure, for whatever reason, patients were excluded from the study.

Prophylactic antibiotic (2 g of cephazolin) was administered intravenously within 1 h before the incision. During the surgical procedures of both groups, normal saline and Ringer's solutions were infused at 1.5 ml/kg/h; fluid infusion was maintained postoperatively for 12 h. Creatinine levels and urinary output demonstrated no significant difference in fluid balance between the groups. Patients received prophylaxis with 2 g of cephazolin intravenously in the morning of POD1 and POD2, or other antibiotics if allergic. Oral antibiotic was administered until the removal of drainages during the post-surgical follow-up. Non-steroidal anti-inflammatory drugs were omitted after surgery. Thus,

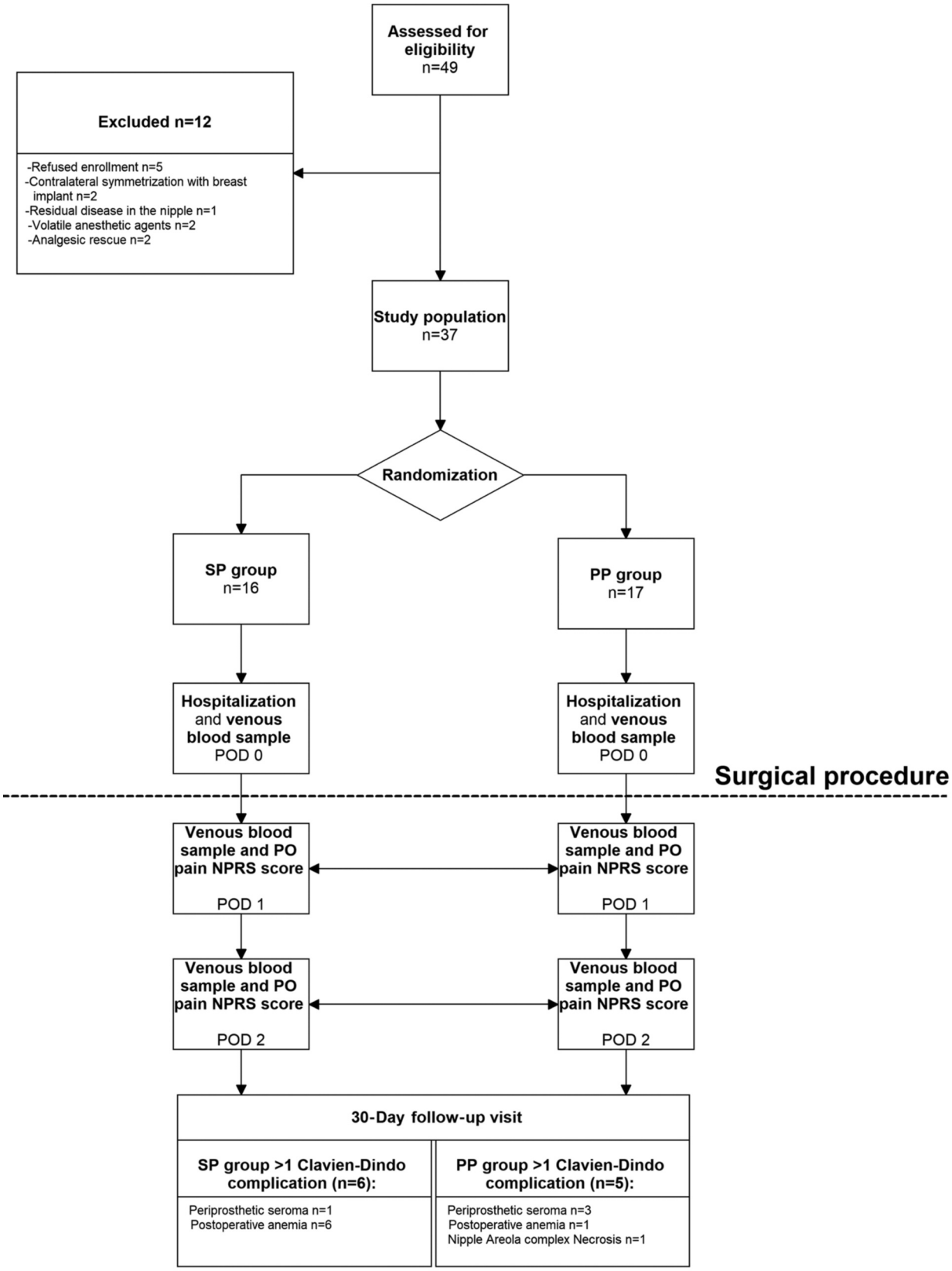


Figure 1. *Flow chart of BIAL2.20 study. PP: Pre-pectoral; POD: postoperative day; PO: postoperative; SP subpectoral; NPRS: numeric pain rating scale.*

Table I. *Demographic and operative data for patients undergoing direct-to-implant pre-pectoral (PP) breast reconstruction with titanium-coated polypropylene mesh versus subpectoral (SP) breast reconstruction. p-Values were calculated with the Mann–Whitney U-test for continuous variables and Fisher's exact test for categorical data.*

| | | SP group (n=16) | PP group (n=17) | *p*-Value |
|---|---|---|---|---|
| Age, years | Mean (range) | 57.49 (48.86-60.46) | 54.10 (46.40-69.11) | 0.401 |
| Number of drains | Mean (range) | 1.67 (1-2) | 1.50 (1-2) | 0.529 |
| Breast implant volume, cc | Mean (range) | 415.33 (350.00-450.00) | 400.67 (331.25-450.00) | 0.719 |
| BMI, kg/m$^2$ | Mean (range) | 24.77 (22.66-33.20) | 22.60 (21.01-26.81) | 0.169 |
| Operative time, min | Mean (range) | 153.45 (132.90-167.36) | 123.26 (105.96-155.11) | 0.250 |
| Contralateral symmetrization, n (%) | Yes | 10 (62.50%) | 12 (70.59%) | 0.721 |
| | No | 6 (37.5%) | 5 (29.41%) | |
| ≥Grade 2 Clavien–Dindo complication, n (%) | Yes | 7 (43.75%) | 5 (29.41%) | 0.481 |
| | No | 9 (56.25%) | 12 (70.59%) | |
| Postoperative anemia, n (%) | Yes | 6 (37.50%) | 1 (5.89%) | 0.039 |
| | No | 10 (62.50%) | 16 (94.11%) | |
| ΔHb, g/dl | Mean (range) | 1.267 (0.85-1.85) | 2.167 (1.40-2.45) | 0.017 |
| Postoperative pain, NPRS | Baseline | 6.5 (4.25-7) | 5 (3-6) | 0.029 |
| | POD1 | 4 (4-5) | 3 (2.75-4.25) | 0.019 |
| | POD2 | 3.5 (3-4.75) | 2 (2-4) | 0.034 |

BMI: Body mass index; ΔHb: postoperative change in hemoglobin ($\Delta Hb=Hb_{POD1}-Hb_{Baseline}$); NPRS: numeric pain rating scale; POD: postoperative day.

postoperative analgesia was achieved through an elastomeric device with tramadol (200 mg in 48 ml every 24 h at a rate of 2 ml/h).

Postoperative pain assessment was carried out using the numeric pain rating scale (NPRS) (0-10), immediately post procedure, on POD1 and POD2, at the time of blood sample collection. All complications within 30 days from surgery were documented and the breast-modified Clavien–Dindo classification was applied (26). Only complications rated as grade 2 or more were analyzed in the study.

*Statistical analysis*. All continuous variables are expressed as medians and interquartile ranges. Preoperative inter-group analysis was performed with the Mann–Whitney *U*-test for major continuous variables. Categorical data are reported as frequencies and percentages, and *p*-values were calculated with Fisher's exact test. Hemoglobin (Hb) levels were calculated as absolute values at baseline and POD1 and as their difference ($\Delta Hb=Hb_{POD1}-Hb_{Baseline}$) and Mann–Whitney *U*-test was performed.

Longitudinal repeated measures of total leukocytes, total lymphocytes, total T-lymphocytes, T-helper lymphocytes, cytotoxic T-lymphocytes, NK cells, and B- lymphocytes were recorded as absolute numbers and percentages, and a two-way analysis of variance test (ANOVA) was applied to determine between-group *p*-values. Prior to analysis, Mauchly's sphericity test, was performed, and when the *p*-value was <0.05, Greenhouse–Geisser correction was applied. The statistical significance cut-off value was defined as $p<0.05$. When variables showed a statistically significant difference in between-group analysas, the Mann–Whitney *U*-test was performed between groups on POD1 and POD2.

## Results

*Preoperative and surgical data*. A total of 49 patients were considered for enrollment. A larger series of patients than the calculated sample size was reached due to the post-enrollment exclusion criteria (*e.g.*, anesthetic regimen; prosthetic contralateral symmetrization).

In fact, following recruitment, five patients refused to enroll (no reason given). Following group allocation, a total of eight patients were excluded from the study. Three patients were removed from the study due to surgical reasons: two underwent prosthetic contralateral symmetrization, and one patient did not undergo a nipple-sparing mastectomy due to residual disease in the nipple margin. Moreover, five patients were removed due to non-surgical reasons: in one case the anesthetic regimen was changed and a further four patients required analgesic rescue therapy not available in the study design. Consequently, the final study cohort resulted in 33 patients divided according to the surgical procedure: SP group, n=16; PP group, n=17. Demographics and procedure variables known as confounding factors are shown in Table I.

There was no statistically significant difference between the groups with regards to age or body mass index ($p=0.401$ and $p=0.169$; respectively). Regarding procedure variables, a shorter mean operative time was reported for the PP group (123.26 *vs*. 153.45; $p=0.250$) without difference in the contralateral symmetrization rate (62.50% *vs*. 70.5%; $p=0.7207$) between the groups. Moreover, no difference was found in the mean number of surgical drains ($p=0.529$), but in the PP group, a larger implant size was placed when compared with the SP group (415.33 *vs*. 400.67; $p=0.719$).

After surgery, Clavien–Dindo complication rates were of grade 2 or more were similar for both groups ($p=0.481$). For the SP group, seven (43.75%) patients experienced complications: There was 1 case of seroma which required

Table II. *Postoperative responses of total leukocytes and leukocyte subsets, and postoperative pain according to the numeric pain rating scale (NPRS) in patients after direct-to-implant pre-pectoral (PP) breast reconstruction with titanium-coated polypropylene mesh versus subpectoral (SP) breast reconstruction. Variables are shown as the median (interquartile range).*

| | Baseline | POD1 | POD2 | *p*-Value* |
|---|---|---|---|---|
| Hb, g/dl | | | | |
| PP | 12.81 (12.05-13.23) | 11.55 (10.7-11.88) | 11.19 (10.25-11.60) | 0.065 |
| SP | 13.46 (13.03-14.40) | 11.27 (10.00-12.05) | 11.25 (10.63-11-85) | |
| Total leukocytes, n/µl | | | | |
| PP | 5.97 (4.93-7.23) | 11.71 (9.66-13.69) | 8.73 (7.49-9.55) | 0.908 |
| SP | 6.35 (5.46-8.065) | 11.20 (8.95-12.16) | 8.70 (7.46-9.98) | |
| B-Lymphocytes, n/µl | | | | |
| PP | 279.87 (157.00-391.50) | 288.87 (159.25-375.50) | 286.73 (192.00-371.00) | 0.567 |
| SP | 254.31 (185.25-364.00) | 232.750 (146.35-279.75) | 316.38 (176.25-344.00) | |
| Total lymphocytes, n/µl | | | | |
| PP | 1,620.87 (1,163.00-2,205.50) | 1,255.07 (902.25-1,693.25) | 1,435.33 (1,020.50-1,625.00) | 0.811 |
| SP | 1,798.875 (1,124.00-2,142.00) | 1,058.500 (639.5-1,351.5) | 1,537.625 (1,015.5-2,020.25) | |
| T-Helper lymphocytes, n/µl | | | | |
| PP | 1,005.73 (833.50-1,323.50) | 733.00 (430.50-1,048.75) | 915.47 (706.00-999.00) | 0.759 |
| SP | 1,155.06 (810.00-1,591.00) | 630.313 (327.75-753.75) | 977.188 (663.50-116.75) | |
| T-Cytotoxic lymphocytes, n/µl | | | | |
| PP | 593.27 (263.00-800.00) | 504.33 (306.00-806.25) | 497.20 (279.00-680.50) | 0.951 |
| SP | 617.13 (477.00-769.00) | 403.81 (237.00-453.25) | 535.06 (303.00-672.25) | |
| NK cell, n/µl | | | | |
| PP | 225.07(114.50-310.00) | 185.67 (103.75-275.5) | 185.600 (106.00-260.00) | 0.239 |
| SP | 308.56 (157.00-414.00) | 254.75 (122.00-363.00) | 236.500 (149.50-303.50) | |
| NPRS | | | | |
| PP | 5.0 (3-6) | 3.0 (2.75-4.25) | 2.0 (2-4) | <0.001 |
| SP | 6.5 (4.25-7) | 4.0 (4-5) | 3.5 (3-4.75) | |

Hb: Hemoglobin; NK: natural killer; NPRS: numeric pain rating scale; POD: postoperative day. *Between-group comparison.

needle aspiration, and six cases of anemia which required pharmacological treatment. In the PP group a total of 5 (29.41%) complications were recorded with three seromas which required needle aspiration, one case of anemia which required pharmacological treatment, and one case of nipple necrosis, which was successfully treated conservatively. Interestingly, a statistically significant difference between the groups was found in postoperative anemia ($p$=0.039), which occurred in 6 patients in SP group, while 1 case of anemia was registered in PP group. Moreover, the decline in Hb was significantly higher for the SP group (PP *vs*. SP group; 1.267 *vs*. 2.167, respectively, $p$=0.0167).

Regarding postoperative pain, the PP group exhibited a lower value of postoperative pain in the analyzed time frame. For both groups, higher median values of NPRS were recorded at the end of the procedure (PP=5 *vs*. SP=6.5), with corresponding lower values at POD1 (3 *vs*. 4) and POD2 (2 *vs*. 3.5). Between-group analysis revealed a statistically significant difference in postoperative NPRS trend ($p$<0.001) (Table II).

*Total leukocytes and lymphocytes: Between-group analysis.* Table II shows a summary of baseline, POD1 and POD2 study data and relative two-way ANOVA results. Baseline value included leukocyte distribution, and lymphocyte subsets.

Two-way ANOVA between-group analysis was performed to evaluate the immunological effect of SP and PP breast reconstruction strategies.

No statistically significant differences were found regarding the immune system and immunological impairment in total leukocytes, total lymphocytes and lymphocyte subgroups, as shown in Table II. Total leukocytes showed a POD1 peak and subsequent fall in both groups, whereas total lymphocytes, B-lymphocytes and T-helper lymphocytes subsets demonstrated a fall on POD1 and a partial recovery on POD2. Finally, NK cells and cytotoxic T-lymphocytes were maintained at steady levels during the observation period.

## Discussion

The systemic stress response to surgery can, through hypothalamic–pituitary–adrenal axis activation, alter immune function and cause a reduction in circulating lymphocytes with a nadir between 2 h and 2 days (27), potentially reducing immunological surveillance (28-30).

In fact, a functioning adaptative immune system is required for tumor immunosurveillance (31), and any congenital or acquired immune defects might result in a higher rate of breast cancer incidence. Circulating lymphocyte and T-lymphocytes play a pivotal role in the adaptative immune response (32, 33), and early postoperative impairment of these subsets has been linked with early postoperative complications (infectious and non-infectious) (33, 34). Moreover, postoperative lymphopenia or a score such as the Systemic Immune-Inflammation Index have been described as promising prognostic factors in surgical oncology (21, 35-40).

In light of this, several protocols have been proposed aiming to reduce surgical stress and length of hospital stay (41-44). During the COVID-19 pandemic, the need to reduce hospital stay, postoperative stress, and consequently postoperative lymphopenia has been even more urgent, leading to a increased popularity of awake breast cancer strategies (2, 45-50).

At the same time, PP DTI protocols were developed with the same aim of reducing postoperative pain to allow an earlier return to function (16). However, little is known regarding the immunological impact of PP DTI reconstruction strategy in the early postoperative period and how any impairment might affect short- and long-term outcomes.

In our previous work, we demonstrated how the use of textured breast implant can lead to a greater depletion of systemic circulating T-lymphocytes when compared with smooth implants (23), and we postulated that different DTI protocols (SP *vs*. PP) may affect the early postoperative immune response.

As expected, the early postoperative immune system was affected differently in terms of leukocyte and lymphocyte populations. Total leukocytes experienced a POD1 peak linked to surgical trauma stress (51). Conversely, total lymphocytes, B-lymphocytes, and T-helper lymphocytes experienced a drop on POD1 and a partial recovery on POD2. This systemic depletion might be linked to the chemotactic stimulus associated with periprosthetic macrophage activation (52), amplifying the periprosthetic Th2 subset immune response (53, 54).

Although previous work on animal models demonstrated how ADM likely influences tissue remodeling and leads to lower levels of inflammatory markers (55, 56), our current work showed how PP DTI reconstruction did not affect early postoperative systemic immunological response when compared with SP DTI reconstruction.

Besides early postoperative immunological response, our current study corroborates previous results regarding postoperative pain, duration of the procedure, and esthetic results, defining the PP DTI protocol as a promising technique. In fact, when compared with the SP group, the PP group exhibited a lower mean procedure time, a lower level of postoperative pain, and reduced blood loss with a larger volume of breast implant.

The finding of a shorter operative time was in line with the data of Sigalove *et al*. (57). These results were easily achieved as the breast implant is usually covered with TCPM while the mastectomy is being performed. Despite the lack of statistical significance in our analysis, we believe that a mean reduction of 30.19 min in the PP DTI procedure might result in the reduction of surgical room occupancy and thus achieve a higher surgical volume (56). However, further studies are needed to underline the potential economic benefit through a cost–benefit analysis. Additionally, the lack of a need for preparation of an SP pocket further reduces surgical anesthesia time, thus reducing surgical systemic stress.

Moreover, as already demonstrated by Zhu *et al*. (58, 59), PP DTI allows a larger breast implant volume when compared to SP DTI reconstruction, providing excellent esthetic results in a single procedure, even in patients with large breasts, without animation deformity (9). Despite the use of larger breast implants, pain assessment resulted in a lower value for the PP group when compared to the SP group. Breast implant weight is a well-known risk factor for postoperative pain due to the mechanical strain exerted by the implants (60). Our results regarding lower postoperative pain in the PP group corroborate previous evidence in the literature (16), allowing a faster return to daily activities and potentially reducing bed occupancy (58). As mentioned before, a future cost–benefit analysis study may provide further evidence supporting the choice between reconstruction strategy (*e.g*., DTI PP *vs*. DTI SP).

Finally, the PP group had a higher Hb level during POD1, with a partial recovery in the SP group during POD2. Interestingly, the SP group experienced a greater ΔHb, and a higher rate of postoperative anemia. Perioperative anemia is a well-known risk factor for prolonged hospitalization, as well as postoperative infectious and non-infectious complications (61), thus PP strategies may represent a safer alternative in patients at risk, such as those receiving systemic medical therapy prior to surgery. In fact, patients undergoing preoperative systemic treatment are at risk for preoperative anemia, which is linked with higher complication rates and worse long-term oncological outcomes in patients undergoing breast reconstruction (61, 62).

It is plausible that a number of limitations might have influenced our results. The first limitation was the small sample size. The sample size was calculated *a priori* to obtain a statistically acceptable power and no statistical differences were found in the demographic and preoperative variables for the two well-matched study groups. Secondly, a solely quantitative assessment of the immune system was carried out, without assessment of lymphocyte activity, circulating inflammatory markers or endocrine response; such analyses are rarely performed in clinical practice and quantitative assessment was specifically chosen to obtain applicable real-life data.

Although many factors may have influenced our results, the well-matched baseline data led us to hypothesize that different DTI techniques do not affect the early postoperative response. Despite rigorous patient selection in order to lower the complication rate, in our clinical trial, PP DTI reconstruction allowed completion of breast reconstruction in a single procedure with lower postoperative pain, lower blood loss and faster return to daily activity.

In conclusion, although to be confirmed in a larger study, our prospective analysis demonstrates that DTI PP breast reconstruction strategy should not be avoided in immunosuppressed patients, and is preferred in patients at risk of postoperative anemia. Moreover, despite the DTI PP group demonstrating a favorable profile in terms of surgical room occupancy, and postoperative pain, further studies are needed to define the more favorable breast reconstruction in term of cost–benefit analysis.

## Conflicts of Interest

All the Authors declare that they have no potential conflicts of interest.

## Authors' Contributions

Study conception and design: Vanni Gianluca and Tacconi Federico; collection of data: Tacconi Federico and Pellicciaro Marco; analysis of data: Vanni Gianluca and Materazzo Marco; interpretation of data: Vanni Gianluca and Marco Materazzo; article draft: Materazzo Marco and Pellicciaro Marco; revision of the article: Amir Sadri.

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## References

1 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin *71(3)*: 209-249, 2021. PMID: 33538338. DOI: 10.3322/caac.21660

2 Vanni G, Materazzo M, Perretta T, Meucci R, Anemona L, Buonomo C, Dauri M, Granai AV, Rho M, Ingallinella S, Tacconi F, Ambrogi V, Chiaravalloti A, Schillaci O, Petrella G and Buonomo OC: Impact of awake breast cancer surgery on postoperative lymphocyte responses. In Vivo *33(6)*: 1879-1884, 2019. PMID: 31662515. DOI: 10.21873/invivo.11681

3 Buonomo O, Granai AV, Felici A, Piccirillo R, De Liguori Carino N, Guadagni F, Polzoni M, Mariotti S, Cipriani C, Simonetti G, Cossu E, Schiaroli S, Altomare V, Cabassi A, Pernazza E, Casciani CU and Roselli M: Day-surgical management of ductal carcinoma in situ (DCIS) of the breast using wide local excision with sentinel node biopsy. Tumori *88(3)*: S48-S49, 2002. PMID: 12365390.

4 Roselli M, Guadagni F, Buonomo O, Belardi A, Ferroni P, Diodati A, Anselmi D, Cipriani C, Casciani CU, Greiner J and Schlom J: Tumor markers as targets for selective diagnostic and therapeutic procedures. Anticancer Res *16(4B)*: 2187-2192, 1996. PMID: 8694541.

5 Buonomo O, Cabassi A, Guadagni F, Piazza A, Felici A, Piccirillo R, Atzei GP, Cipriani C, Schiaroli S, Mariotti S, Guazzaroni MN, Cossu E, Simonetti G, Pernazza E, Casciani CU and Roselli M: Radioguided-surgery of early breast lesions. Anticancer Res *21(3C)*: 2091-2097, 2001. PMID: 11501831.

6 Orsaria P, Chiaravalloti A, Fiorentini A, Pistolese C, Vanni G, Granai AV, Varvaras D, Danieli R, Schillaci O, Petrella G and Buonomo OC: PET Probe-Guided Surgery in Patients with Breast Cancer: Proposal for a Methodological Approach. In Vivo *31(1)*: 101-110, 2017. PMID: 28064227. DOI: 10.21873/invivo.11031

7 Orsaria P, Chiaravalloti A, Caredda E, Marchese PV, Titka B, Anemona L, Portarena I, Schillaci O, Petrella G, Palombi L and Buonomo OC: Evaluation of the Usefulness of FDG-PET/CT for Nodal Staging of Breast Cancer. Anticancer Res *38(12)*: 6639-6652, 2018. PMID: 30504372. DOI: 10.21873/anticanres.13031

8 Orsaria P, Varvaras D, Vanni G, Pagnani G, Scaggiante J, Frusone F, Granai AV, Petrella G and Buonomo OC: Nodal status assessment in breast cancer: strategies of clinical grounds and quality of life implications. Int J Breast Cancer *2014*: 469803, 2014. PMID: 24672730. DOI: 10.1155/2014/469803

9 Buonomo OC, Morando L, Materazzo M, Vanni G, Pistilli G, Palla L, Di Pasquali C and Petrella G: Comparison of round smooth and shaped micro-textured implants in terms of quality of life and aesthetic outcomes in women undergoing breast reconstruction: a single-centre prospective study. Updates Surg *72(2)*: 537-546, 2020. PMID: 32062785. DOI: 10.1007/s13304-020-00721-w

10 Galimberti V, Vicini E, Corso G, Morigi C, Fontana S, Sacchini V and Veronesi P: Nipple-sparing and skin-sparing mastectomy: Review of aims, oncological safety and contraindications. Breast *34(Suppl 1)*: S82-S84, 2017. PMID: 28673535. DOI: 10.1016/j.breast.2017.06.034

11 Bielli A, Bernardini R, Varvaras D, Rossi P, Di Blasi G, Petrella G, Buonomo OC, Mattei M and Orlandi A: Characterization of a new decellularized bovine pericardial biological mesh: Structural and mechanical properties. J Mech Behav Biomed Mater *78*: 420-426, 2018. PMID: 29223730. DOI: 10.1016/j.jmbbm.2017.12.003

12 American Society of Plastic Surgery: 2018 Plastic Surgery Statistics Report 2018. Available at: https://www.plasticsurgery.org/documents/News/Statistics/2018/plastic-surgery-statistics-full-report-2018.pdf [Last accessed on September 28, 2021]

13 Salibian AA, Frey JD and Karp NS: Strategies and considerations in selecting between subpectoral and prepectoral breast reconstruction. Gland Surg *8(1)*: 11-18, 2019. PMID: 30842923. DOI: 10.21037/gs.2018.08.01

14 Buonomo OC, Varvaras D, Montuori M, Vanni G, Venditti D, Elia S, Santurro L, Granai AV, Petrella G and Rossi P: One-stage immediate implant-based breast reconstruction, using biological matrices after conservative mastectomies: Preliminary experience of the University Hospital of Tor Vergata, Rome. Chir *28(6)*: 221-226, 2015.

15 Bozzuto LM, Bartholomew AJ, Tung S, Sosin M, Tambar S, Cox S, Perez-Alvarez IM, King CA, Chan MC, Pittman TA and Tousimis EA: Decreased postoperative pain and opioid use

following prepectoral *versus* subpectoral breast reconstruction after mastectomy: A retrospective cohort study: Pain after pre- *versus* subpectoral reconstruction. J Plast Reconstr Aesthet Surg *74(8)*: 1763-1769, 2021. PMID: 33451949. DOI: 10.1016/j.bjps.2020.12.009

16 Lee JS, Park E, Lee JH, Lee J, Park HY, Yang JD and Jung TD: A prospective comparison study of early functional outcomes after implant-based breast reconstruction: subpectoral versus prepectoral technique. Ann Palliat Med *10(3)*: 2520-2529, 2021. PMID: 33691448. DOI: 10.21037/apm-20-1550

17 Beilin B, Shavit Y, Trabekin E, Mordashev B, Mayburd E, Zeidel A and Bessler a: The effects of postoperative pain management on immune response to surgery. Anesthesia & Analgesia: 822-827, 2020. DOI: 10.1213/01.ANE.0000078586.82810.3B

18 Lee SK, Choi MY, Bae SY, Lee JH, Lee HC, Kil WH, Lee JE, Kim SW and Nam SJ: Immediate postoperative inflammation is an important prognostic factor in breast cancer. Oncology *88(6)*: 337-344, 2015. PMID: 25721153. DOI: 10.1159/000368985

19 Cho JS, Lee MH, Kim SI, Park S, Park HS, Oh E, Lee JH and Koo BN: The effects of perioperative anesthesia and analgesia on immune function in patients undergoing breast cancer resection: a prospective randomized study. Int J Med Sci *14(10)*: 970-976, 2017. PMID: 28924368. DOI: 10.7150/ijms.20064

20 Vanni G, Tacconi F, Sellitri F, Ambrogi V, Mineo TC and Pompeo E: Impact of awake videothoracoscopic surgery on postoperative lymphocyte responses. Ann Thorac Surg *90(3)*: 973-978, 2010. PMID: 20732526. DOI: 10.1016/j.athoracsur.2010.04.070

21 Cabrera AG, Dyamenahalli U, Gossett J, Prodhan P, Morrow WR, Imamura M, Jaquiss RD and Bhutta AT: Preoperative lymphopenia is a predictor of postoperative adverse outcomes in children with congenital heart disease. J Thorac Cardiovasc Surg *138(5)*: 1172-1179, 2009. PMID: 19660346. DOI: 10.1016/j.jtcvs.2009.06.016

22 Yamamoto M, Saito H, Uejima C, Tanio A, Takaya S, Ashida K and Fujiwara Y: Combined pre- and postoperative lymphocyte count accurately predicts outcomes of patients with colorectal cancer. Dig Surg *36(6)*: 487-494, 2019. PMID: 30219805. DOI: 10.1159/000492340

23 Vanni G, Materazzo M, Pellicciaro M, Amir S, Tacconi F, Ambrogi V and Buonomo OC: Breast textured implants determine early T-helper impairment: BIAL2.20 study. Anticancer Res *41(4)*: 2123-2132, 2021. PMID: 33813423. DOI: 10.21873/anticanres.14984

24 Tønnesen E, Höhndorf K, Lerbjerg G, Christensen NJ, Hüttel MS and Andersen K: Immunological and hormonal responses to lung surgery during one-lung ventilation. Eur J Anaesthesiol *10(3)*: 189-195, 1993. PMID: 8495681.

25 Piazza A, Adorno D, Poggi E, Borrelli L, Buonomo O, Pisani F, Valeri M, Torlone N, Camplone C, Monaco PI, Fraboni D and Casciani CU: Flow cytometry crossmatch: a sensitive technique for assessment of acute rejection in renal transplantation. Transplant Proc *30(5)*: 1769-1771, 1998. PMID: 9723274. DOI: 10.1016/s0041-1345(98)00423-0

26 Panhofer P, Ferenc V, Schütz M, Gleiss A, Dubsky P, Jakesz R, Gnant M and Fitzal F: Standardization of morbidity assessment in breast cancer surgery using the Clavien Dindo Classification. Int J Surg *12(4)*: 334-339, 2014. PMID: 24486930. DOI: 10.1016/j.ijsu.2014.01.012

27 Finnerty CC, Mabvuure NT, Ali A, Kozar RA and Herndon DN: The surgically induced stress response. JPEN J Parenter Enteral Nutr *37(5 Suppl)*: 21S-29S, 2013. PMID: 24009246. DOI: 10.1177/0148607113496117

28 Ielpo B, Pernaute AS, Elia S, Buonomo OC, Valladares LD, Aguirre EP, Petrella G and Garcia AT: Impact of number and site of lymph node invasion on survival of adenocarcinoma of esophagogastric junction. Interact Cardiovasc Thorac Surg *10(5)*: 704-708, 2010. PMID: 20154347. DOI: 10.1510/icvts.2009.222778

29 Ielpo B, Mazzetti C, Venditti D, Buonomo O and Petrella G: A case of metachronous splenic metastasis from renal cell carcinoma after 14 years. Int J Surg *8(5)*: 353-355, 2010. PMID: 20438874. DOI: 10.1016/j.ijsu.2010.04.006

30 Veronesi U, Viale G, Paganelli G, Zurrida S, Luini A, Galimberti V, Veronesi P, Intra M, Maisonneuve P, Zucca F, Gatti G, Mazzarol G, De Cicco C and Vezzoli D: Sentinel lymph node biopsy in breast cancer: ten-year results of a randomized controlled study. Ann Surg *251(4)*: 595-600, 2010. PMID: 20195151. DOI: 10.1097/SLA.0b013e3181c0e92a

31 Goff SL and Danforth DN: The role of immune cells in breast tissue and immunotherapy for the treatment of breast cancer. Clin Breast Cancer *21(1)*: e63-e73, 2021. PMID: 32893093. DOI: 10.1016/j.clbc.2020.06.011

32 Chiricozzi A, Faleri S, Saraceno R, Bianchi L, Buonomo O, Chimenti S and Chimenti MS: Tofacitinib for the treatment of moderate-to-severe psoriasis. Expert Rev Clin Immunol *11(4)*: 443-455, 2015. PMID: 25666451. DOI: 10.1586/1744666X.2015.1013534

33 Haas OA: Primary immunodeficiency and cancer predisposition revisited: Embedding two closely related concepts into an integrative conceptual framework. Front Immunol *9*: 3136, 2019. PMID: 30809233. DOI: 10.3389/fimmu.2018.03136

34 Torrance HD, Pearse RM and O'Dwyer MJ: Does major surgery induce immune suppression and increase the risk of postoperative infection? Curr Opin Anaesthesiol *29(3)*: 376-383, 2016. PMID: 26963469. DOI: 10.1097/ACO.0000000000000331

35 Cho O, Chun M, Kim SW, Jung YS and Yim H: Lymphopenia as a potential predictor of ipsilateral breast tumor recurrence in early breast cancer. Anticancer Res *39(8)*: 4467-4474, 2019. PMID: 31366546. DOI: 10.21873/anticanres.13620

36 Ferroni P, Roselli M, Spila A, D'Alessandro R, Portarena I, Mariotti S, Palmirotta R, Buonomo O, Petrella G and Guadagni F: Serum sE-selectin levels and carcinoembryonic antigen mRNA-expressing cells in peripheral blood as prognostic factors in colorectal cancer patients. Cancer *116(12)*: 2913-2921, 2010. PMID: 20336782. DOI: 10.1002/cncr.25094

37 Hua X, Long ZQ, Zhang YL, Wen W, Guo L, Xia W, Zhang WW and Lin HX: Prognostic value of preoperative systemic immune-inflammation index in breast cancer: a propensity score-matching study. Front Oncol *10*: 580, 2020. PMID: 32373539. DOI: 10.3389/fonc.2020.00580

38 Ferroni P, Palmirotta R, Spila A, Martini F, Formica V, Portarena I, Del Monte G, Buonomo O, Roselli M and Guadagni F: Prognostic value of carcinoembryonic antigen and vascular endothelial growth factor tumor tissue content in colorectal cancer. Oncology *71(3-4)*: 176-184, 2006. PMID: 17652942. DOI: 10.1159/000106072

39 D'Alessandro R, Roselli M, Ferroni P, Mariotti S, Spila A, Aloe S, Carone MD, Abbolito MR, Carlini S, Perri P, Ricciotti A, Botti C, Conti F, Vici P, Chiappetta NR, Cognetti F, Buonomo O and Guadagni F: Serum tissue polypeptide specific antigen (TPS): a complementary tumor marker to CA 15-3 in the management of breast cancer. Breast Cancer Res Treat *68(1)*: 9-19, 2001. PMID: 11678313. DOI: 10.1023/a:1017903724176

40 Dupont G, Flory L, Morel J, Lukaszewicz AC, Patoir A, Presles E, Monneret G and Molliex S: Postoperative lymphopenia: An independent risk factor for postoperative pneumonia after lung cancer surgery, results of a case-control study. PLoS One *13(10)*: e0205237, 2018. PMID: 30321194. DOI: 10.1371/journal.pone.0205237

41 Ackerman RS, Hirschi M, Alford B, Evans T, Kiluk JV and Patel SY: Enhanced REVENUE after surgery? A cost-standardized enhanced recovery pathway for mastectomy decreases length of stay. World J Surg *43(3)*: 839-845, 2019. PMID: 30456482. DOI: 10.1007/s00268-018-4850-0

42 Vanni G, Pellicciaro M, Materazzo M, Dauri M, D'angelillo RM, Buonomo C, De Majo A, Pistolese C, Portarena I, Mauriello A, Servadei F, Giacobbi E, Chiaravalloti A and Buonomo OC: Awake breast cancer surgery: strategy in the beginning of COVID-19 emergency. Breast Cancer *28(1)*: 137-144, 2021. PMID: 32734327. DOI: 10.1007/s12282-020-01137-5

43 Tinti F, Lai S, Noce A, Rotondi S, Marrone G, Mazzaferro S, Di Daniele N and Mitterhofer AP: Chronic kidney disease as a systemic inflammatory syndrome: update on mechanisms involved and potential treatment. Life (Basel) *11(5)*: 419, 2021. PMID: 34063052. DOI: 10.3390/life11050419

44 Di Daniele N, Noce A, Vidiri MF, Moriconi E, Marrone G, Annicchiarico-Petruzzelli M, D'Urso G, Tesauro M, Rovella V and De Lorenzo A: Impact of Mediterranean diet on metabolic syndrome, cancer and longevity. Oncotarget *8(5)*: 8947-8979, 2017. PMID: 27894098. DOI: 10.18632/oncotarget.13553

45 Vanni G, Buonomo OC, Gualtieri P and Merra G: Editorial - Breast cancer: awake surgery as strategy during second COVID-19 lockdown? Eur Rev Med Pharmacol Sci *24(24)*: 13101-13102, 2020. PMID: 33378066. DOI: 10.26355/eurrev_202012_24218

46 Vanni G, Materazzo M, Santori F, Pellicciaro M, Costesta M, Orsaria P, Cattadori F, Pistolese CA, Perretta T, Chiocchi M, Meucci R, Lamacchia F, Assogna M, Caspi J, Granai AV, DE Majo A, Chiaravalloti A, D'Angelillo MR, Barbarino R, Ingallinella S, Morando L, Dalli S, Portarena I, Altomare V, Tazzioli G and Buonomo OC: The effect of Coronavirus (COVID-19) on breast cancer teamwork: a multicentric survey. In Vivo *34(3 Suppl)*: 1685-1694, 2020. PMID: 32503830. DOI: 10.21873/invivo.11962

47 Buonomo OC, Materazzo M, Pellicciaro M, Caspi J, Piccione E and Vanni G: Tor Vergata University-hospital in the beginning of COVID-19-Era: Experience and recommendation for breast cancer patients. In Vivo *34(3 Suppl)*: 1661-1665, 2020. PMID: 32503826. DOI: 10.21873/invivo.11958

48 Vanni G, Pellicciaro M, Materazzo M, Palombi L and Buonomo OC: Breast cancer diagnosis in Coronavirus-era: Alert from Italy. Front Oncol *10*: 938, 2020. PMID: 32574281. DOI: 10.3389/fonc.2020.00938

49 Noce A, Santoro ML, Marrone G, D'Agostini C, Amelio I, Duggento A, Tesauro M and Di Daniele N: Serological determinants of COVID-19. Biol Direct *15(1)*: 21, 2020. PMID: 33138856. DOI: 10.1186/s13062-020-00276-1

50 Vanni G, Legramante JM, Pellicciaro M, DE Carolis G, Cotesta M, Materazzo M, Buonomo C, Farinaccio A, Santori F, Saraceno F, Ielpo B, Aiello F, Paganelli C, Grande M, DE Andreis G, Chiocchi M, Palombi L and Buonomo OC: Effect of lockdown in surgical emergency accesses: Experience of a COVID-19 hospital. In Vivo *34(5)*: 3033-3038, 2020. PMID: 32871849. DOI: 10.21873/invivo.12137

51 Desborough JP: The stress response to trauma and surgery. Br J Anaesth *85(1)*: 109-117, 2000. PMID: 10927999. DOI: 10.1093/bja/85.1.109

52 Anderson JM, Rodriguez A and Chang DT: Foreign body reaction to biomaterials. Semin Immunol *20(2)*: 86-100, 2008. PMID: 18162407. DOI: 10.1016/j.smim.2007.11.004

53 Mariani E, Lisignoli G, Borzì RM and Pulsatelli L: Biomaterials: Foreign bodies or tuners for the immune response? Int J Mol Sci *20(3)*: 636, 2019. PMID: 30717232. DOI: 10.3390/ijms20030636

54 Kadin ME, Morgan J, Xu H, Epstein AL, Sieber D, Hubbard BA, Adams WP Jr, Bacchi CE, Goes JCS, Clemens MW, Medeiros LJ and Miranda RN: IL-13 is produced by tumor cells in breast implant-associated anaplastic large cell lymphoma: implications for pathogenesis. Hum Pathol *78*: 54-62, 2018. PMID: 29689246. DOI: 10.1016/j.humpath.2018.04.007

55 Bernardini R, Varvaras D, D'Amico F, Bielli A, Scioli MG, Coniglione F, Rossi P, Buonomo OC, Petrella G, Mattei M and Orlandi A: Biological acellular pericardial mesh regulated tissue integration and remodeling in a rat model of breast prosthetic implantation. J Biomed Mater Res B Appl Biomater *108(2)*: 577-590, 2020. PMID: 31094057. DOI: 10.1002/jbm.b.34413

56 Leong M, Basu CB and Hicks MJ: Further evidence that human acellular dermal matrix decreases inflammatory markers of capsule formation in implant-based breast reconstruction. Aesthet Surg J *35(1)*: 40-47, 2015. PMID: 25568233. DOI: 10.1093/asj/sju014

57 Sigalove S, Maxwell GP, Sigalove NM, Storm-Dickerson TL, Pope N, Rice J and Gabriel A: Prepectoral implant-based breast reconstruction: Rationale, indications, and preliminary results. Plast Reconstr Surg *139(2)*: 287-294, 2017. PMID: 28121858. DOI: 10.1097/PRS.0000000000002950

58 Glasberg SB: The economics of prepectoral breast reconstruction. Plast Reconstr Surg *140(6S Prepectoral Breast Reconstruction)*: 49S-52S, 2017. PMID: 29166348. DOI: 10.1097/PRS.0000000000004051

59 Zhu L, Mohan AT, Abdelsattar JM, Wang Z, Vijayasekaran A, Hwang SM, Tran NV and Saint-Cyr M: Comparison of subcutaneous *versus* submuscular expander placement in the first stage of immediate breast reconstruction. J Plast Reconstr Aesthet Surg *69(4)*: e77-e86, 2016. PMID: 26922050. DOI: 10.1016/j.bjps.2016.01.006

60 Govrin-Yehudain O, Matanis Y and Govrin-Yehudain J: Reduced pain and accelerated recovery following primary breast augmentation with lightweight breast implants. Aesthet Surg J *38(10)*: 1092-1096, 2018. PMID: 29579148. DOI: 10.1093/asj/sjy071

61 Muñoz M, Franchini M and Liumbruno GM: The post-operative management of anaemia: more efforts are needed. Blood Transfus *16(4)*: 324-325, 2018. PMID: 29517972. DOI: 10.2450/2018.0036-18

62 Sarhane KA, Flores JM, Cooney CM, Abreu FM, Lacayo M, Baltodano PA, Ibrahim Z, Alrakan M, Brandacher G and Rosson GD: Preoperative anemia and postoperative outcomes in immediate breast reconstructive surgery: a critical analysis of 10,958 patients from the ACS-NSQIP database. Plast Reconstr Surg Glob Open *1(5)*: e30, 2013. PMID: 25289224. DOI: 10.1097/GOX.0b013e3182a18c6f

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