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Breast Textured Implants Determine Early T-helper Impairment: BIAL2.20 Study

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Abstract. *Background/Aim: Surgical stress has been correlated with higher rate of postoperative complications. Breast implants' surfaces (textured or smooth) represent an immunological stimulus. Our prospective study (BIAL2.20) evaluated post-operative leukocytes response at baseline and postoperative day (POD) 1 and 2 after implant-based breast reconstruction. Patients and Methods: Between January and July 2020, 41 patients underwent reconstruction with textured (n=23) or smooth (n=18) implants. A full blood count and lymphocyte subsets were collected before surgery, on POD1 and POD2. Data were evaluated as difference and relative difference from baseline by two-way analysis of variance test (2-way-ANOVA). Mann-Whitney U-test was performed at each POD, whenever between-group 2-way-ANOVA reached statistical significance. Results: Within-group-analysis showed statistically significant total leukocytosis in both groups. Within-group-analysis of lymphocytes subsets demonstrated statistically significant lymphopenia in the textured group for T-lymphocytes, and T-helper cells. Between-group-analysis showed statistically significant lymphopenia in T-helper subsets in the textured group at POD1 and POD2, when compared with the smooth group. Conclusion: Textured implants demonstrated a statistically significant impairment of T-helper trend during POD1 and POD2 when compared to smooth implants by between-group 2-way-ANOVA.*

In surgical oncology, emerging evidence suggests that surgical stress may result in postoperative complications (1-5), as well as a higher risk of locoregional and distant disease relapse (2, 6-8).

Despite the popularization of conservative approaches (9-12), such as awake surgery and oncoplastic procedures (13-15), mastectomy followed by breast reconstruction is still necessary for a significant number of patients (16-18). This procedure results in higher surgical postoperative stress and surgical complications (16, 19-21) compared to breast conserving surgery (1, 2).

The features of breast implants may play a pivotal role in postoperative surgical stress (22-25). In particular, implant characteristics (shape and surface texture) may represent a stimulus for the immunological system of the patients (24-26). As demonstrated before, some textured implants (macrotextured) have been correlated with a higher risk of late onset breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), and they were withdrawn from the market (24, 27). In fact, current theories about the onset of BIA-ALCL link chronic inflammatory periprosthetic microenvironment with monoclonal T-Helper expansion (28).

Despite available evidence in literature regarding the kinetics of the T-lymphocyte response to persistent antigens (27), data on breast implants' surface, early periprosthetic environment and potential early immunological impairment are still missing. There have been descriptions of an oscillatory pattern in white blood cells after implant based breast reconstruction, in particular repeated prosthetic reconstruction has shown a decreased T-cell count (27, 29, 30), but the evidence of the impact of different prosthetic surface (textured *vs.* smooth) on postoperative immune system is still missing. Emerging evidence in literature suggests that early postoperative lymphopenia represents a risk factor for early postoperative complications (31, 32), and long term oncological disease control (33).

Our prospective study (BIAL2.20) aimed to evaluate early T-helper impairment on postoperative day (POD) 1 and 2 after textured *versus* smooth implant-based breast reconstruction.

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Key Words: Breast cancer, breast reconstruction, breast implant, immune function, immunological, surgery, Macrotextured implant, lymphocytes, leukocytes, white blood cell.

Patients and Methods

Study design and patients' selection. A single institution, prospective observational trial (textured implants group *versus* smooth implants group) (Figure 1) was undertaken. The local institutional review board approved the study with the code name of BIAL2.20 and registration number of CEI n° 15/20. BIAL2.20 was funded by the Ministry of Health (Fund N° CUP E84E19002740006). Sample size was calculated following preliminary data obtained from an observational study assuming a 10% difference between the groups in the absolute number of T-helper on POD2 as primary endpoint. After having set alpha error at 0.05 with power analysis of 80%, sample size was established to 32 patients, accounting 16 for each group. To avoid any detrimental effect on the quality of life due to the different implants, we decided not to randomize patients (10, 18). Group allocation was decided intraoperatively by the plastic surgeon, according to expected aesthetic results, leaving the breast surgeon and the other physicians involved in the study absolutely unaware before surgery of the kind of breast prosthesis to be implanted (single blinded).

The primary inclusion criteria for the BIAL2.20 study were a previous diagnosis of non-metastatic breast cancer treated with mastectomy within one year and immediate two-stage breast reconstruction procedure with tissue expander (CPX™ 4 Tissue Expander, Medium Height, Style 8200 Mentor®, Johnson & Johnson, New Brunswick, NJ, USA). Other inclusion criteria were age between 18 and 70 years old, female gender, no usage of anti-inflammatory or β-agonists drugs during the 2 months prior to the operation. Patients with a history of connective tissue disease were excluded from the study. Moreover, patients who underwent a mastectomy following breast-conserving treatment for breast cancer and/or radiotherapy were excluded as well (11, 15, 34). Due to the nature of the study and T-helper subset POD 2 difference set as primary endpoint, the observational period was terminated at 30 days from the surgical procedure. According to these prerequisites and requirements, the BIAL2.20 study was activated in January 2020 and terminated in July 2020.

Preoperative assessment. Before recruitment, all patients were counselled regarding each type of surgical approach and signed specific written-informed consent for participation in the study. One-week prior to the surgery, all patients underwent a plastic surgery consultation. During the visit, the plastic surgeon chose both micro-textured and smooth implants tailored upon patients. As stated before, definitive decision about the kind of prosthesis were extemporaneously made during the procedure.

Venous blood sampling time points. At 7.30 a.m., prior to surgery, a venous blood sample was taken through the antecubital peripheral vein of the arm. On POD 1 and POD 2, samples were collected at the same hour. This specific time interval was selected as there are numerous studies in the literature that use this frame to evaluate lymphocyte response according to different surgical procedures (3, 10, 35-38).

Full blood count, total leukocyte, total lymphocytes, total T-lymphocytes, T-helper lymphocytes, T-cytotoxic lymphocytes, natural killer (NK) cell, and B-cell lymphocytes were collected in absolute numbers and percentages. Samples were processed using a cell counter (Coulter Beckmann, MedLab, Cupertino, CA, USA). BD FACS Calibur (BD Biosciences, Franklin Lakes, NJ, USA) was employed for three-color cytometry (39). Lymphocyte subsets were obtained by incubating blood samples for 30 minutes with monoclonal antibodies at 4°C. The percentage of subsets was calculated by differential gating after three-colors coloring.

Surgical techniques. All patients were placed in supine *decubitus* position and underwent CPX™ 4 Tissue Expander removal. Tissue expander volume was recorded. During the reconstruction, textured or smooth implant was placed in the sub-muscular plane, patients were divided into the study groups according to the prosthesis chosen by the surgeon, according to the expected aesthetic result (textured group *vs*. smooth group). All patients underwent inferior surgical capsulotomy of the implant pocket. At the end of the procedure, one or more suction drainages were placed according to the surgeon's choice and removed when the serous fluid loss was less than 30 ml/24 h. Contralateral symmetrization techniques without breast implants [mastopexy or contralateral mirroring (15)] were admitted to the study, but no contralateral breast implants procedure were allowed in the study. To reduce the risk of potential *bias* due to the 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 (3, 10, 35-38, 40). Whenever the anesthetic regimen changed during the procedure for whatever reason, patients were excluded from the study.

Prophylactic antibiotic, Cephazolin 2 Gr IV, was administered within one hour before the incision. During the surgical procedure, fluid infusion at 1.5 ml/kg/h of normal saline and Ringer's solution were used in both groups of patients; fluid infusion was maintained postoperatively for 12 h. Creatinine levels and urinary output demonstrated no significant difference in fluid balance between the groups. Patients were given intravenous prophylaxis with Cefazolin 2 g IV in the morning of POD1 and POD2. Drains were removed during the post-surgical follow-up and oral antibiotic was administered until removal. Non-steroidal anti-inflammatory drugs were forbidden after surgery. Thus, 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 made using a Visual Analogic Scale (0-10) for pain on POD 1 (VAS_1) and POD 2 (VAS_2) at the time of blood sample collection. All complications within 30 days of surgery were collected and Breast Modified Clavien-Dindo classification was applied (41, 42). Only the complications rated as ≥2 were analyzed in the study.

Statistical analysis. All continuous variables are expressed as medians and interquartile ranges (IQR). Preoperative inter-group analysis was performed with the Mann-Whitney *U*-test for major continuous variables. Categorical data were reported as frequencies and percentages and *p*-values were calculated with Fisher's exact test. Longitudinal repeated measures of total leukocyte, total lymphocytes, total T-lymphocytes, T-helper lymphocytes, T-cytotoxic lymphocytes, NK cells, and B-cell lymphocytes were recorded as absolute numbers and percentages. Difference and relative difference [Δx=PODx-baseline; Δ%x=(PODx-baseline/baseline)*100; respectively] were calculated for repeated measures and two-way analysis of variance test (Two-way-ANOVA) was applied to determine within-group, between-groups and interaction *p*-values. Prior analysis, Mauchly's Sphericity Test was performed, and when *p*-value was <0.05, Greenhouse-Geisser correction was applied. The statistically significant cut-off value was defined as

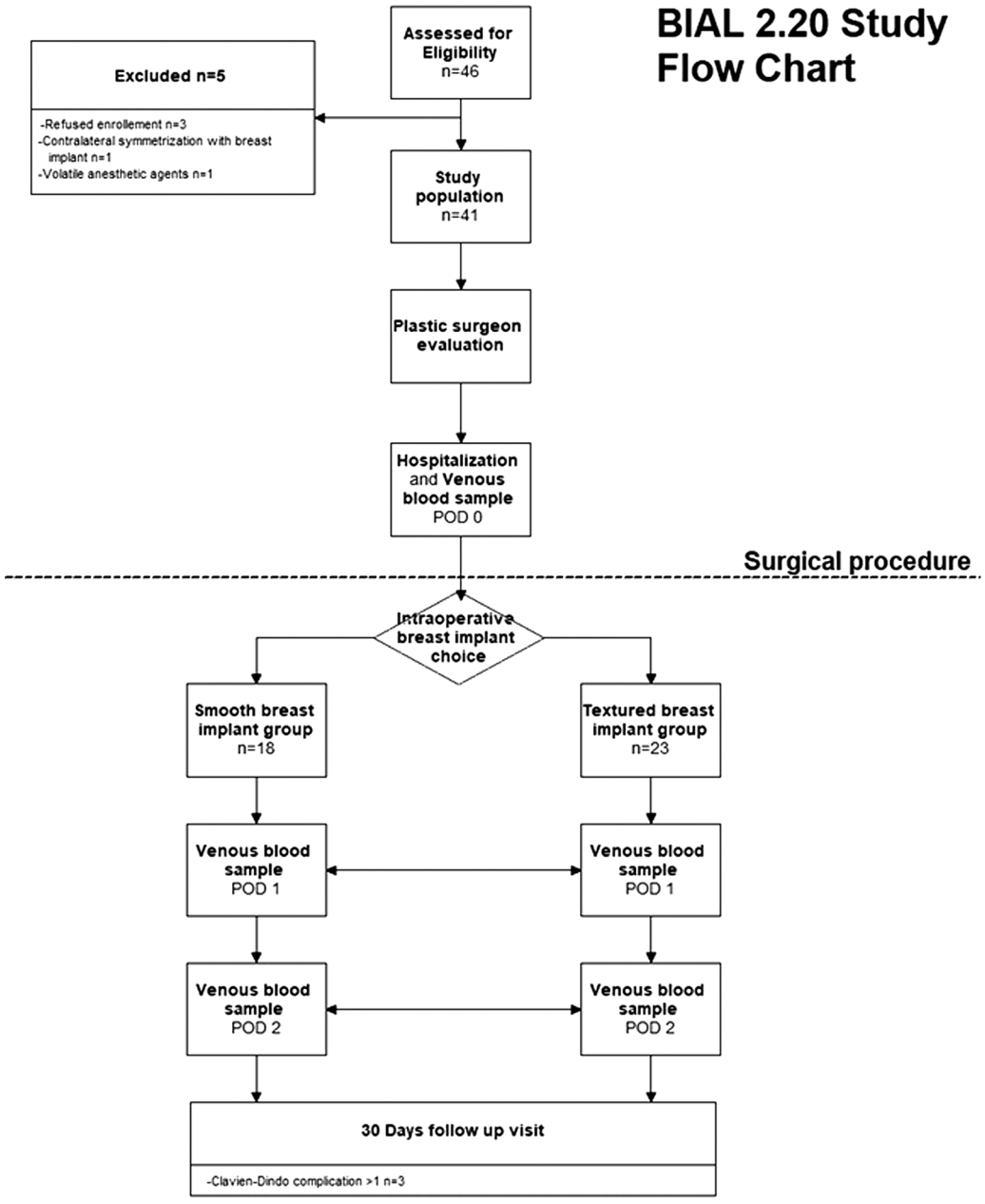

Figure 1. *Flow chart of BIAL2.20 study. POD: Postoperative day.*

$p<0.05$. When variables showed a statistically significant difference in between analysis, the Mann-Whitney *U*-test was performed between-group on POD1 and POD2.

Results

Preoperative and surgical data. A total of 46 patients were considered for enrollment. We preferred to include in the study a greater than the predicted sample size due to the lack of randomization and the existence of exclusion criteria following enrollment or surgical procedure (*e.g*. anesthetic regimen; prosthetic contralateral symmetrization).

Following recruitment, 3 patients withdrew (no reason given). After allocation, 2 patients were excluded from the study because one patient had received contralateral symmetrization with prosthesis and another received volatile anesthetic agents. Consequently, the final study group population considered for the study consisted on 41 patients divided into two groups (textured group, n=23; smooth

Table I. *Demographic and operative data. All continuous data are shown as mean and range in brackets. Tissue expander volume and implant volume are shown as median and interquartile range (IQR). P-value was calculated with the Mann–Whitney U-test for continuous variables and Fisher's exact test for categorical data.*

Baseline findings (n TOT=41)	Textured group (n=23)	Smooth group (n=18)	*p*-Value
Age (years)	57.32 (49.76-66.67)	41.58 (30.68-46.09)	0.819
Number of drains (median)	1 (1-2)	1 (1-2)	0.850
Tissue expander volume (ml)	350 (275-550)	350 (275-550)	0.819
Bi volume (ml)	415 (350-525)	445 (220-580)	0.558
BMI (Value)	24.00 (21.53-28.3)	25.09 (20.89-36.05)	0.965
Symmetrisation (Yes)	12/23 (52.17%)	5/18 (27.78%)	0.201
Vas1	3.01	2.91	0.741
Vas2	2.05	2.18	0.694
≥2 Clavien-Dindo Complication (yes)	2/23 (8.70%)	1/18 (5.56%)	1.000

BMI: Body mass index; VAS: visual analogic scale for pain; VAS1: VAS during POD 1; VAS2: during POD 2.

group, n=18). Demographic and operative data, considered confounding factors, are listed in Table I, showing no statistical difference when compared between groups (43).

Age and body mass index (BMI) analysis reported casual distribution between the groups (p=0.965; p=0.819, respectively).

Procedure analysis did not show a statistically significant difference in the symmetrization rate between the two cohorts of patients (p=0.201). Moreover, no difference was found in the chosen breast implants median volume (p=0.558), tissue expander median volume (p=0.819), and median number of surgical drains (p=0.742).

After surgery, no statistical difference was present in postoperative pain between POD1 (VAS_1 p=0.741) and POD 2 (VAS_2 p=0.694), nor when considering ≥2 Clavien-Dindo complications (p=1.000). Textured group experienced 2 complications: one case of seroma and one of post-operative mild anemia (POD2 hemoglobin 9.7 gr/dl). Both complications were conservatively treated (Clavien-Dindo II). In smooth group, one seroma occurred successively, requiring needle aspiration (Clavien-Dindo III).

Total leukocytes and lymphocytes subsets change. Table II shows a summary of the study results. Baseline data regarding leukocyte distribution and lymphocyte subsets did not show any statistically significant difference between textured and smooth groups. Table III exhibits differences, relative differences, and p-values of two-way-ANOVA.

Within-group analysis. Within-group analysis showed statistical results for total leukocytes in the textured group and smooth group (p<0.001 *vs.* p=0.001, respectively). Both groups showed a statistically significant increase on POD1 (textured group p<0.001; smooth group p=0.003) when compared with baseline data, and subsequent decrease toward baseline values on POD2 (Figure 2).

Conversely, in the textured group the total lymphocytes demonstrated a significant drop at POD1 with subsequent partial rebound on POD2 with a statistically significant value in the within-analysis (p=0.002). The drop on POD1 was not demonstrated in total lymphocytes of the smooth group with a flat curve (p=0.572) (Figure 3).

Difference and relative difference of T-lymphocytes showed a trend similar to that of total lymphocytes in both groups. The within-group analysis of T-lymphocytes showed that absolute and relative differences were statistically significant in the textured implants (p=0.001), but not in the smooth group (p=0.637).

T-helper lymphocyte trends are displayed in Figure 4. Within-group analysis displayed a statistically significant distribution in the textured group only (p<0.001). Conversely, T-cytotoxic lymphocytes, NK cells, and B-lymphocytes did not exhibit a statistically significant difference in within-group analysis.

Between-group analysis. Two-way-ANOVA between-group analysis was carried out to underline the early immunological difference between textured and smooth groups. In total leukocytes, similar trends with a peak on POD1 and subsequent fall were found in both groups (Figure 2) with no statistically significant difference (p=0.640). Neither total lymphocytes (p=0.247), nor T-lymphocytes (p=0.302) (Figure 3) showed different trends between groups.

Notably, absolute and relative differences in T-helper lymphocytes demonstrated a statistically significant trend in the between-group analysis (p=0.045). T-helper lymphocytes registered a larger drop on POD1 among the textured group in comparison with the smooth group, as shown in Figure 4. The Mann-Whitney U-test did not demonstrate a significant difference on POD 1 in T-helper lymphocytes [1058.05 (799.5-1348.5) *vs.* 748.60 (541-880), p=0.967 and 48.11 (41.5-53) *vs.* 42.80 (42-43.6), p=0.938, respectively]. A

Table II. *Preoperative and postoperative responses of total leukocytes and leukocytes subsets, variables are shown as median and Interquartile range (IQR) in brackets.*

	Baseline	POD 1	POD 2
Total leukocytes (n 10^9/l)			
Textured group	6.49 (5.43-7.5125)	11.88 (9.0125-13.835)	8.71 (7.5625-9.555)
Smooth group	4.94 (3.42-5.83)	9.13 (8.5-9.36)	7.098 (5.6-7.23)
Total lymphocytes (n 10^9/l)			
Textured group	2,239.46 (1,600-2,862.25)	1,571.75 (1,000-2,000)	2,193.50 (1,800-2,325)
Smooth group	1,747.60 (1,300-2,100)	1,490.20 (800-1,800)	1,464.00 (1,286-1,600)
T-lymphocyte (n 10^9/l)			
Textured group	1,725.62 (1,196.25-2,148.75)	1,090.11 (751.25-1,380.75)	1,635.86 (1,147-1,846.75)
Smooth group	1,405.40 (1,016-1,928)	1,171.20 (594-1,646)	1,168.80 (1,020-1,455)
T-lymphocyte (%)			
Textured group	73.63 (70-81.5)	67.86 (63.5-78)	74.18 (71.00-82.25)
Smooth group	79.80 (78-92)	78.20 (74-91)	79.60 (79.00-91.00)
T-helper lymphocytes (n 10^9/l)			
Textured group	1,058.05 (799.5-1,348.5)	613.5 (405-754.25)	1,031.54 (798.25-1,126.75)
Smooth group	748.60 (541-880)	620.20 (252-759)	622.80 (493-716)
T-helper lymphocytes (%)			
Textured group	48.11 (41.5-53)	38.43 (30.5-45)	47.43 (41.75-54.25)
Smooth group	42.80 (42-43.6)	38.80 (31-42)	42.20 (38-45)
T-cytotoxic lymphocytes (n 10^9/l)			
Textured group	653.73 (287.25-745)	459.86 (238-570.75)	588.00 (298-743)
Smooth group	625.60 (469-986)	522.40 (343-827)	518.00 (509-696)
T-cytotoxic lymphocytes (%)			
Textured group	26.83 (21-31.75)	28.21 (20-35.5)	25.89 (18.75-30.25)
Smooth group	35.4 (36-47)	38.00 (43-46)	36.00 (40-44)
NK cell (n 10^9/l)			
Textured group	282.07 (138-405.25)	255.86 (144.25-368.75)	234.96 (123.75-304.25)
Smooth group	151.00 (111-119)	104.60 (64-92)	127.20 (64-112)
NK cell (%)			
Textured group	12.52 (6-16)	16.86 (9.5-20.25)	11.07 (6.01-13.25)
Smooth group	9.00 (6-9)	7.80 (4.05-11.20)	8.80 (4.45-9.73)
B-lymphocytes (n 10^9/l)			
Textured group	251.79 (134-376.25)	222.89 (125.08-298.75)	314.36 (183.75-376.69)
Smooth group	184.60 (52-160)	210.80 (88-112)	165.60 (80-151)
B-lymphocytes (%)			
Textured group	11.72 (10-14)	14.89 (11.75-17.5)	14.50 (11-17.25)
Smooth group	10.80 (2-12)	13.40 (5-14)	11.60 (5-12)

NK cell: Natural killer cell.

statistically significant difference was found on POD 2 in absolute numbers and percentages between groups [1,031.54 (798.25-1,126.75) *vs*. 622.80 (493-716), p=0.018 and 47.43% (41.75-54.25) *vs*. 42.20% (38-45), p=0.040, respectively]. No further statistical difference in the between-analysis was found regarding the other subsets (T-cytotoxic lymphocytes, NK cells, B-lymphocytes), as presented in Table III.

Discussion

T-helper lymphocytes are the central mediator of adaptative immune response by producing effector cytokines, playing a crucial role in adaptive immune responses to infective, autoimmune or allergic diseases (44, 45). The systemic response to surgical stress through hypothalamic-pituitary-adrenal axis activation could determine an impaired immune function and specifically T-helper lymphopenia with a nadir between 2 hours and 2 days (2, 4, 5).

Despite postoperative lymphopenia being widely proposed as a risk factor for postoperative complications (4), only recently has data demonstrated how postoperative lymphopenia represents an independent risk factor for infectious and not-infectious early postoperative complications (5, 32). Moreover, in oncological procedures early postoperative lymphopenia was described as a potential predictor of ipsilateral breast cancer recurrence (46), and lower five-year disease-specific survival rates in colorectal cancer (33, 47).

Several surgical and anaesthesiologic protocols have been designed with the purpose of reducing the impact of surgical and anaesthetic trauma in many surgical specialties (3, 9, 35,

Table III. *Postoperative differences in total leukocytes and leukocyte subsets values are shown as difference from baseline as absolute number (Δ) and percentage (Δ%) in brackets. NK cell: Natural killer cell. Lymphocytes and lymphocyte subsets Δ were evaluated with two-way-ANOVA for repeated measures. *statistically significant.*

	Δ POD1 (n 10^9/l)	(Δ%)	Δ POD2 (n 10^9/l)	(Δ%)	Within-group *p*-value	Between-group *p*-Value	Interaction *p*-Value
Total leukocytes						0.640	<0.001*
Textured group	5.39	(83.05)	3.32	(51.15)	<0.001*		
Smooth group	4.19	(84.82)	2.91	(58.86)	0.001*		
Total lymphocytes (n 10^9/l)						0.247	0.073
Textured group	–667.71	(–29.82)	2,861.21	(127.76)	0.002*		
Smooth group	–257.4	(–14.73)	1,721.40	(98.50)	0.572		
T-lymphocyte (n 10^9/l)						0.302	0.372
Textured group	–635.51	(–36.83)	2,271.37	(131.62)	0.001*		
Smooth group	–234.2	(–16.66)	1,403.00	(99.82)	0.637		
T-helper lymphocytes (n 10^9/l)						0.045*	0.004*
Textured group	–444.55	(–42.02)	1,476.09	(139.51)	<0.001*		
Smooth group	–128.4	(–17.15)	751.20	(100.34)	0.798		
T-cytotoxic lymphocytes (n 10^9/l)						0.717	0.557
Textured group	–193.87	(–29.66)	781.87	(119.60)	0.206		
Smooth group	–103.2	(–16.50)	621.20	(99.30)	0.201		
NK cell (n 10^9/l)						0.713	0.426
Textured group	–26.21	(–9.29)	261.17	(92.59)	0.063		
Smooth group	–46.4	(–30.73)	173.60	(114.97)	0.656		
B-lymphocytes (n 10^9/l)						0.128	0.735
Textured group	–28.9	(–11.48)	343.26	(136.33)	0.055		
Smooth group	26.2	(14.19)	139.40	(75.51)	0.901		

36, 40, 48). However, despite a growing trend towards breast conserving surgery (34, 40, 49), mastectomy plus reconstruction is still required in some patients, leading to specific complications, such as BIA-ALCL (16, 19, 22, 50).

The emerging problem of BIA-ALCL has demonstrated that breast implants surface and it's bacterial colonization could determine subclinical inflammation, T-helper monoclonal expansion and subsequent development of BIA-ALCL's pathogenesis (37, 51, 52). The pathogenesis of BIA-ALCL underlies an amplified immune response, especially in textured implants, with features of a chronic allergic reaction in a susceptible patient (53). Despite these immunological theories, crosstalk between mesenchymal peri-prosthetic cell and T-helper/BIA-ALCL cells is still poorly understood (54).

Our results are consistent with existing theories and previous data from the literature. In fact, we demonstrated that early crosstalk between host and textured breast implant surfaces determines an early immunological impairment of the T-helper population. In our cohort, T-helper subsets in the textured group displayed a decrease on POD 1 with statistically significant value at two-way-ANOVA between-analysis when compared with smooth implants. Interestingly, this reduction takes place despite the expected increment of total leukocytes count exhibited at POD 1 as a physiological response to surgical trauma (1).

We hypothesized that this behavior may be triggered by a higher chemotactic stimulus driven by periprosthetic M1-M2 macrophage immune response against textured prosthesis (55, 56). These cells attract T-helper cells toward the periprosthetic microenvironment (57) and direct their terminal differentiation into Th2 subsets eliciting an amplified immune response with features of a chronic allergic reaction (53). We postulated that this recruitment could eventually determine systemic depletion of T-helper population in our samples with higher risk of postoperative complications (5, 32, 58), and potential immunological impairment (59, 60).

We are aware that our research has some limitations. First of all, this study has a non-randomized design. Grouping allocation was intraoperative, decided by plastic surgeon. This may have introduced a potential selection bias. However, we think that lack of randomization was an ethical choice, driven by the risk of a detrimental effect on patients' aesthetics and quality of life outcomes. Nevertheless, we achieved two well-matched study groups. In particular, demographic, and preoperative variables as age, BMI, contralateral symmetrization, number of drains, and complication rates did not differ between the two populations. Other postoperative variables that could affect postoperative lymphocyte response like postoperative pain or early complications were evaluated with no significant impact. Additionally, confounding variables such as anaesthetic regimen, postoperative analgesia,

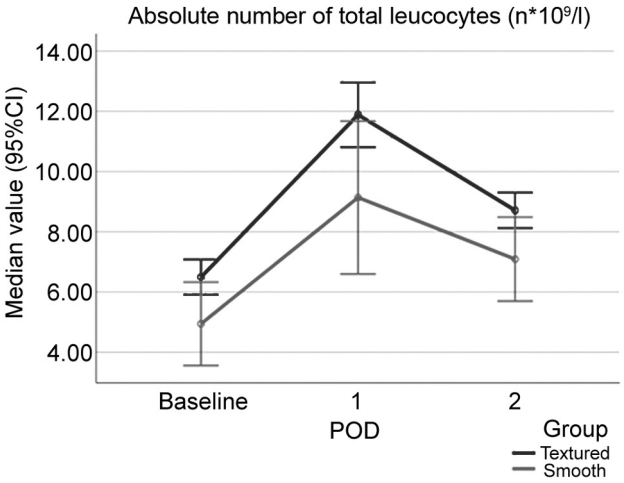

Figure 2. *Absolute number of total leukocytes in the early postoperative period. All Values are shown as median with 95%CI. POD: Postoperative day; 95%CI: 95% confidence interval.*

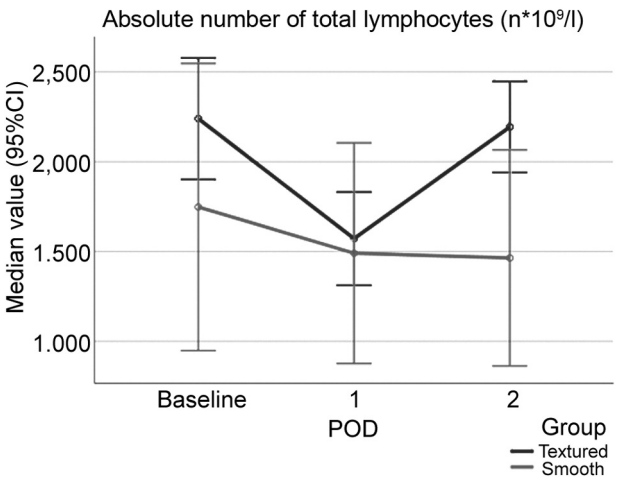

Figure 3. *Absolute number of Total Lymphocytes in the early postoperative period. All Values are shown as median with 95%CI. POD: Postoperative day; 95%CI: 95% confidence interval.*

and previous implant tissue expander were selected to reduce as much as possible any other confounding factors. Second limitation was the small sample size, which could have affected the power of our study. However, the sample size was calculated prior to recruitment to assure a statistically acceptable power in detecting intergroup differences. Third limitation of the current analysis is the sole quantitative assessment without information about lymphocyte activity as well as circulating inflammatory markers and endocrine response. However, data regarding lymphocyte activity or inflammation biomarkers, such as cytokine or chemokine, are rarely evaluated in the postoperative clinical practice.

Although many other factors could have altered our results, the well-matched baseline data led us to postulate that breast implants surface could have played a major role in postoperative lymphocytes impairment through lymphocyte periprosthetic recruitment.

Implant based breast reconstruction can produce excellent aesthetic results with reduced operating times compared to microsurgical reconstruction. Our prospective study demonstrates that textured implants result in an early immunological impairment with a T-helper cell reduction. In conclusion, if confirmed in a larger study, our current findings regarding impaired immunological function in the early postoperative period may have practical relevance in frail patients.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

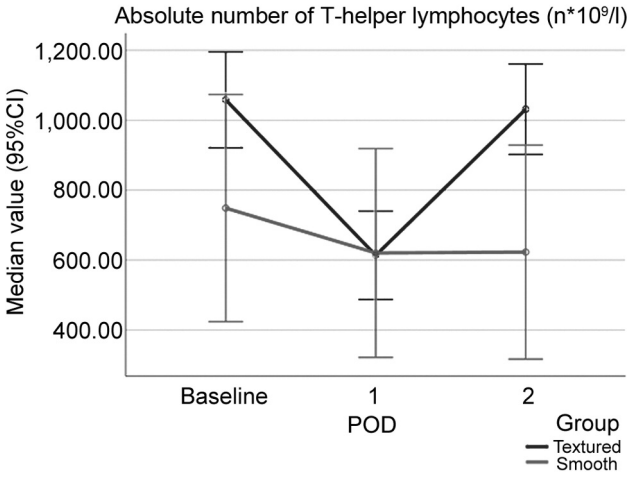

Figure 4. *Absolute number of T-helper Lymphocytes in the early postoperative period. All Values are shown as median with 95%CI. POD: Postoperative day; 95%CI: 95% confidence interval.*

Authors' Contributions

Study conception and design: Vanni Gianluca, Materazzo Marco, Buonomo Oreste Claudio; Collection of data: Tacconi Federico, Pellicciaro Marco; Analysis of data: Vanni Gianluca, Materazzo Marco; Interpretation of data: Buonomo Oreste Claudio, Vanni Gianluca; Article draft: Materazzo Marco, Vanni Gianluca, Ambrogi Vincenzo; Critical revision: Amir Sadri, Ambrogi Vincenzo; Critical revision of literature: Amir Sadri, Materazzo Marco.

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References

1 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

2 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

3 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

4 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

5 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

6 Retsky M, Demicheli R and Hrushesky WJ: Does surgery induce angiogenesis in breast cancer? Indirect evidence from relapse pattern and mammography paradox. Int J Surg *3(3)*: 179-187, 2005. PMID: 17462282. DOI: 10.1016/j.ijsu.2005.08.002

7 Kim R: Effects of surgery and anesthetic choice on immunosuppression and cancer recurrence. J Transl Med *16(1)*: 8, 2018. PMID: 29347949. DOI: 10.1186/s12967-018-1389-7

8 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

9 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

10 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

11 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.

12 Quaranta V, Manenti G, Bolacchi F, Cossu E, Pistolese CA, Buonomo OC, Carotenuto L, Piconi C and Simonetti G: FEM analysis of RF breast ablation: Multiprobe *versus* cool-tip electrode. Anticancer Res *27(2)*: 775-784, 2007. PMID: 17465202.

13 Vanni G, Materazzo M, Pellicciaro M, Morando L, Portarena I, Anemona L, D'Angelillo MR, Barbarino R, Chiaravalloti A, Meucci R, Perretta T, Deiana C, Orsaria P, Caspi J, Pistolese CA and Buonomo OC: Does age matter? Estimating risks of locoregional recurrence after breast-conservative surgery. In Vivo *34(3)*: 1125-1132, 2020. PMID: 32354901. DOI: 10.21873/invivo.11884

14 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

15 Calì Cassi L, Vanni G, Petrella G, Orsaria P, Pistolese C, Lo Russo G, Innocenti M and Buonomo O: Comparative study of oncoplastic *versus* non-oncoplastic breast conserving surgery in a group of 211 breast cancer patients. Eur Rev Med Pharmacol Sci *20(14)*: 2950-2954, 2016. PMID: 27460720

16 Jonczyk MM, Jean J, Graham R and Chatterjee A: Trending towards safer breast cancer surgeries? Examining acute complication rates from a 13-year NSQIP analysis. Cancers (Basel) *11(2)*: 2019. PMID: 30795637. DOI: 10.3390/cancers11020253

17 American Society of Plastic Surgery: 2018 Plastic Surgery Statistics Report, 2018. Available at: https://www.plasticsurgery.org [Last accessed on April 2, 2020]

18 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

19 Wilkins EG, Hamill JB, Kim HM, Kim JY, Greco RJ, Qi J and Pusic AL: Complications in postmastectomy breast reconstruction: One-year outcomes of the Mastectomy Reconstruction Outcomes Consortium (MROC) Study. Ann Surg *267(1)*: 164-170, 2018. PMID: 27906762. DOI: 10.1097/SLA.0000000000002033

20 Robertson SA, Jeevaratnam JA, Agrawal A and Cutress RI: Mastectomy skin flap necrosis: challenges and solutions. Breast Cancer (Dove Med Press) *9*: 141-152, 2017. PMID: 28331365. DOI: 10.2147/BCTT.S81712

21 Vanni G, Materazzo M, Pellicciaro M, Ingallinella S, Rho M, Santori F, Cotesta M, Caspi J, Makarova A, Pistolese CA and Buonomo OC: Breast cancer and COVID-19: The effect of fear on patients' decision-making process. In Vivo *34(3 Suppl)*: 1651-1659, 2020. PMID: 32503825. DOI: 10.21873/invivo.11957

22 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

23 Buonomo OC, Varvaras D, Montuori M, Vanni G, Venditti D, Elia S, Santurro L, Granai A V, 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*: 221-226, 2015.

24 Mempin M, Hu H, Chowdhury D, Deva A and Vickery K: The A, B and C's of Silicone Breast Implants: Anaplastic large cell lymphoma, biofilm and capsular contracture. Materials (Basel) *11(12)*: 2018. PMID: 30486500. DOI: 10.3390/ma11122393

25 Marra A, Viale G, Pileri SA, Pravettoni G, Viale G, De Lorenzi F, Nolè F, Veronesi P and Curigliano G: Breast implant-associated anaplastic large cell lymphoma: A comprehensive review. Cancer Treat Rev *84*: 101963, 2020. PMID: 31958739. DOI: 10.1016/j.ctrv.2020.101963

26 Román M, Sala M, Domingo L, Posso M, Louro J and Castells X: Personalized breast cancer screening strategies: A systematic review and quality assessment. PLoS One *14(12)*: e0226352, 2019. PMID: 31841563. DOI: 10.1371/journal.pone.0226352

27 Shanklin DR and Smalley DL: Kinetics of T lymphocyte responses to persistent antigens. Exp Mol Pathol *80(1)*: 26-37, 2006. PMID: 16125699. DOI: 10.1016/j.yexmp.2005.04.002

28 Collett DJ, Rakhorst H, Lennox P, Magnusson M, Cooter R and Deva AK: Current Risk Estimate of Breast Implant-Associated Anaplastic Large Cell Lymphoma in Textured Breast Implants. Plast Reconstr Surg *143(3S A Review of Breast Implant-Associated Anaplastic Large Cell Lymphoma)*: 30S-40S, 2019. PMID: 30817554. DOI: 10.1097/PRS.0000000000005567

29 Hart AJ, Skinner JA, Winship P, Faria N, Kulinskaya E, Webster D, Muirhead-Allwood S, Aldam CH, Anwar H and Powell JJ: Circulating levels of cobalt and chromium from metal-on-metal hip replacement are associated with CD8+ T-cell lymphopenia. J Bone Joint Surg Br *91(6)*: 835-842, 2009. PMID: 19483243. DOI: 10.1302/0301-620X.91B6.21844

30 Catelas I, Lehoux EA, Hurda I, Baskey SJ, Gala L, Foster R, Kim PR and Beaulé PE: Do patients with a failed metal-on-metal hip implant with a pseudotumor present differences in their peripheral blood lymphocyte subpopulations? Clin Orthop Relat Res *473(12)*: 3903-3914, 2015. PMID: 26324830. DOI: 10.1007/s11999-015-4466-8

31 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

32 Quintanilla-González L, Torres-Villalobos G and Hinojosa-Azaola A: Risk factors for development of early infectious and noninfectious complications in systemic lupus erythematosus patients undergoing major surgery. Lupus *27(12)*: 1960-1972, 2018. PMID: 30185095. DOI: 10.1177/0961203318799188

33 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

34 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

35 Mineo TC, Sellitri F, Vanni G, Gallina FT and Ambrogi V: Immunological and inflammatory impact of non-intubated lung metastasectomy. Int J Mol Sci *18(7)*: 2017. PMID: 28686211. DOI: 10.3390/ijms18071466

36 Vanni G, Tacconi F, Mineo TC and Pompeo E: Awake thoracoscopic treatment of spontaneous pneumothorax. *In*: Awake thoracic surgery. Bentham Science Publishers Ltd., pp. 130-140, 2012.

37 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

38 Tacconi F, Vanni G and Pompeo E: Systemic host response in awake thoracic surgery. In: Awake Thoracic Surgery. Bentham Science Publishers Ltd., pp. 19-33, 2012.

39 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

40 Calì Cassi L, Biffoli F, Francesconi D, Petrella G and Buonomo O: Anesthesia and analgesia in breast surgery: The benefits of peripheral nerve block. Eur Rev Med Pharmacol Sci *21(6)*: 1341-1345, 2017. PMID: 28387892

41 Winter R, Haug I, Lebo P, Grohmann M, Reischies FMJ, Cambiaso-Daniel J, Tuca A, Rienmüller T, Friedl H, Spendel S, Forbes AA, Wurzer P and Kamolz LP: Standardizing the complication rate after breast reduction using the Clavien-Dindo classification. Surgery *161(5)*: 1430-1435, 2017. PMID: 28043695. DOI: 10.1016/j.surg.2016.11.028

42 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

43 Sada A, Day CN, Hoskin TL, Degnim AC, Habermann EB and Hieken TJ: Mastectomy and immediate breast reconstruction in the elderly: Trends and outcomes. Surgery *166(4)*: 709-714, 2019. PMID: 31395398. DOI: 10.1016/j.surg.2019.05.055

44 Zhu J: T Helper Cell Differentiation, Heterogeneity, and Plasticity. Cold Spring Harb Perspect Biol *10(10)*: 2018. PMID: 28847903. DOI: 10.1101/cshperspect.a030338

45 Zhu J and Paul WE: CD4 T cells: fates, functions, and faults. Blood *112(5)*: 1557-1569, 2008. PMID: 18725574. DOI: 10.1182/blood-2008-05-078154

46 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

47 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

48 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

49 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

50 Isik O, Kaya E, Dundar HZ and Sarkut P: Surgical Site Infection: Re-assessment of the risk factors. Chirurgia (Bucur) *110(5)*: 457-461, 2015. PMID: 26531790

51 Noguchi M, Minami M, Earashi M, Taniya T, Miyazaki I I, Mizukami Y, Nonomura A, Nishijima H, Takanaka T, Kawashima H, Saito Y, Takashima C, Nakamura S, Michigishi T and Yokoyama K: Pathologic assessment of surgical margins on frozen and permanent sections in breast conserving surgery. Breast Cancer *2(1)*: 27-33, 1995. PMID: 11091529. DOI: 10.1007/BF02966893

52 Ali HR, Chlon L, Pharoah PD, Markowetz F and Caldas C: Patterns of immune infiltration in breast cancer and their clinical implications: A gene-expression-based retrospective study. PLoS Med *13(12)*: e1002194, 2016. PMID: 27959923. DOI: 10.1371/journal.pmed.1002194

53 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

54 Orciani M, Caffarini M, Torresetti M, Campanati A, Parodi P, Di Benedetto G and Di Primio R: Breast implant texturization does not affect the crosstalk between MSC and ALCL cells. Inflammation *42(2)*: 721-730, 2019. PMID: 30446982. DOI: 10.1007/s10753-018-0930-4

55 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

56 Goodman SB and Ma T: Cellular chemotaxis induced by wear particles from joint replacements. Biomaterials *31(19)*: 5045-5050, 2010. PMID: 20398931. DOI: 10.1016/j.biomaterials.2010.03.046

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

58 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

59 Machida H, De Zoysa MY, Takiuchi T, Hom MS, Tierney KE and Matsuo K: Significance of monocyte counts at recurrence on survival outcome of women with endometrial cancer. Int J Gynecol Cancer *27(2)*: 302-310, 2017. PMID: 27922978. DOI: 10.1097/IGC.0000000000000865

60 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

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