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Regulation of The Inflammatory Profile of Blood Serum in Human Breast Cancer: Prominent Roles for TNF-alpha and RPR Pathways on Breast Surgery

Ahmad Za'im Muhtar Mahfuddin*[a], Yan Wisnu Prajoko[b], Mohamad Sofyan Harahap[c], Banundari Rachmawati[d], Widya Istanto Nurcahyo[c]

[a]*Department of General Surgery, Dr. Kariadi Hospital-Diponegoro University, Semarang, Indonesia*

[b]*Department of Oncology Surgery, Dr. Kariadi Hospital-Diponegoro University, Semarang, Indonesia*

[c]*Department of Anesthesiology, Dr. Kariadi Hospital-Diponegoro University, Semarang, Indonesia*

[d]*Department of Clinical Pathology, Dr. Kariadi Hospital-Diponegoro University, Semarang, Indonesia*

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ABSTRACT

Background: The study aimed to compare the effects of the combination of PECS Block II with GA and GA alone on the inflammation levels in breast cancer, measured by Tumor Necrosis Factor-Alpha (TNF-α) and the red blood cell distribution width to platelet ratio (RPR).

Methods: This experimental analytical study which was a parallel randomized control trial was done on 48 breast cancer patients who underwent breast removal surgery at Dr. Kariadi Hospital from August to October, 2023. Patients were randomly assigned to two groups, control (GA only) and treatment (PECS Block II + GA). Demographic data were obtained preoperatively, with blood samples collected 24 hours before and after surgery. TNF-α levels were analyzed using enzyme-linked immunosorbant assay (ELISA), while RPR were obtained from complete blood counts. Independent t and mann-whitney tests were used, with a P-value <0.05 considered to be significant.

Results: Postoperative TNF-α levels were similar in both groups (8.15 ± 5.31 vs 6.21 ± 5.58; P=0,135), but the difference between TNF-α levels was significantly higher in the treatment group (-5.08 ± 3.70; P = 0.001). Postoperative RPR levels were higher in the control group than in the treatment group (0,64 ± 0,28 vs 0,50 ± 0,20; P=0,031), where the difference between RPR levels was higher in the treatment group (-0,07 ± 0,19; P = 0,037).

Conclusion: Inflammatory biomarkers, in the form of TNF-α and RPR in breast cancer surgery were found to be lower with the usage of the combination of PECS Block II with general anesthesia than with general anesthesia only.

INTRODUCTION

Breast cancer is the cancer with the highest incidence in women in the world, around 20% with an increasing trend over the year. In Indonesia, breast cancer is the most common type of cancer, both in women and in the entire population, with an estimated incidence of 40.3 per 100,000 women or 48,998 new cases per year.[1] The principle of breast cancer therapy is to reduce the possibility of recurrence and the risk of metastasis, with the main modality being surgery.[2] Surgery is known to trigger inflammation and immunosuppression due to tissue damage, causing the secretion of a proinflammatory response. Previous research has reported that monocytes and

***Address for correspondence:**
Ahmad Za'im Muhtar Mahfuddin
Department of General Surgery, Dr. Kariadi Hospital-Diponegoro University, Semarang, Indonesia
Email : zaim.muhtar234@gmail.com

macrophages release pro-inflammatory cytokines in the form of TNF-α, IL-1, and IL-6.[3] Excessive expression of TNF-α has been correlated with increased tumor cell proliferation, higher malignancy rates, increased occurrence of metastases, and poor general prognosis for patients. Apart from the pro-inflammatory mediators already mentioned, other biomarkers have been found to increase in breast cancer, such as RPR (Red Cell Distribution Width to Platelet Ratio), a ratio between RDW (Red Cell Distribution Width) and platelet, which according to previous research is a sign of poor prognosis, and a marker for recurrence and metastasis of breast cancer. This study sought to determine the benefit of TNF-α and RPR markers in breast cancer.

Combination of anesthesia and tissue stress during surgery can suppress immune functions affecting the postoperative immune-inflammatory response.[7] This response is formed through changes in the secretion of pro-tumorigenic cytokines.[8] Anesthesia technique commonly used in breast cancer surgery is PECS II block combined with general anesthesia (GA). This technique provides blocks to the axillary and intercostal nerves and has been proven to reduce postoperative pain compared to administering GA alone.[9]

Behind the anti-pain benefits of GA, there is a negative effect on cancer prognosis, where an increase in neutrophils and a decrease in lymphocytes has been reported to occur in patients operated on with GA alone compared to patients that were given the PECS Block combination.[10] Research on the effect of PECS II and GA on proinflammatory biomarkers is still limited. This research aims to study the effects of the GA and PECS II combination compared to GA alone on TNF-α levels and RPR in breast cancer patients undergoing breast removal surgery.

METHODS

This is an experimental, analytical study with a parallel randomized control trial (RCT). Breast cancer patients who underwent breast removal surgery at RSUP Dr. Kariadi in August – October 2023 were screened for enrollment. This period of time was chosen following previous studies suggesting that breast cancer diagnosis is related to seasonal variations. Breast cancer diagnosis rates have been found to be higher notably at the end of August, with other studies showing a steep peak of breast cancer diagnosis between autumn and winter (September until December).[11,12] The inclusion criteria were I) age 18 to 59 years of age; II) patients in a good physical status without any systemic disease or functional limitations according to the classification of the American Society of Anesthesiologists of ASA 1 (patients healthy and normal, BMI <30 kg/m^2, non-smoking, good exercise tolerance) and ASA 2 (patients with mild systemic disease, without functional limitations and well-controlled disease)(13); III) patients with early breast cancer (stages I-II according to American Joint Committee on Cancer); IV) patients undergoing breast cancer removal surgery with preoperative TNF-α and RPR levels; V) able to communicate verbally; and VI) those who agreed to participate in the research by signing a consent form. The exclusion criteria were: I) Patients with allergies or contraindications to the drugs in the study; II) local infections at the site of PECS Block II administration; and III) patients with a history of blood coagulation disorders. The study was carried out in accordance with our institusional guidelines and regulations, with all of the participating patients having signed an informed consent form before enrollment.

We calculated the sample size using a two-sample t-test sample size formula, with a 5% precision, a type-1 error of 5%, the variance of the outcome of 10, and the minimum detectable difference between the two groups of 12. Based on our calculation, with the additional 10% of predicted drop-out rate, a minimum of 24 subjects per group were needed in this study. The patients were randomly assigned to two groups using a random number table, where the allocated numbers were sealed in opaque enevelopes and opened before the surgery. The control group received only general anesthesia when they underwent breast removal surgery, while the treatment group received a combination of PECS block II with general anesthesia. The PECS block II procedure was done using the ultrasound (US) guided method, with the site of injection located inferior to the 4th rib bone unilateral to the operating side. The needle was inserted, and the tip was placed between the anterior serratus and minor pectoral muscles. After the needle was placed, we aspirated the syringe to confirm the position of the tip. We then injected 30 cc of isobaric bupivacaine 0,25% to block the nerve. The TNF-a biomarker levels and RPR values were obtained from the blood samples collected 24 hours before and 24 hours after surgery and were examined using the automatic hematologic analyzer and ELISA method.

The Statistical Package for the Social Sciences (SPSS) for Windows, version 26,0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. Continous data are expressed as means with standar deviation (SD). Normally distributed data were analyzed using independent-t test; otherwise, the mann-whitney test was used. A P-value of <0,05 was considered as significant.

RESULTS

A total of 48 subjects were randomly assigned to two groups with 24 subjects in each group. All of the subjects finished the study without any drop-out, and were included in the final analysis.

The mean age of the research subjects was 50.33 ± 11.53 years old; the mean body weight of the research subjects was 61.54 ± 12.89 kilograms; the mean height of the research subjects was 1.57 ± 0.07 meter; the mean BMI of the research subjects was 24.89 ± 4.56 kg/m^2, with the mean duration of surgery being 91.93 ± 50.60 minutes; the mean MAP was 86.23 ± 9.32 mmHg and the mean fentanyl consumption was 90.83 ± 19.98 mL.

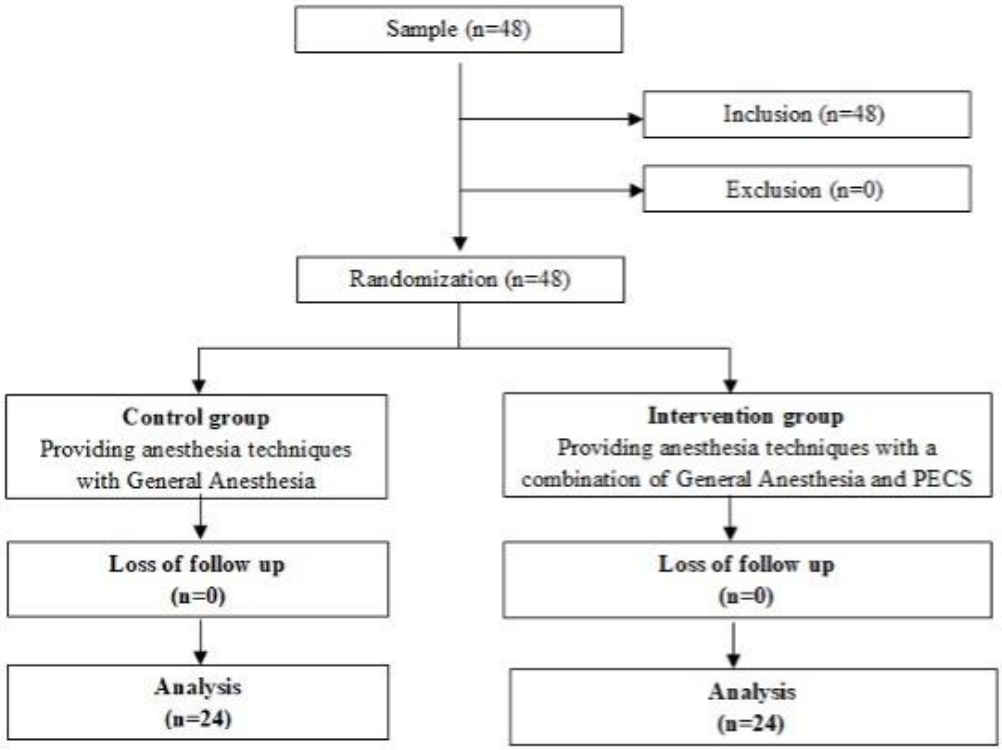

Figure 1. Research Design Diagram

Table 1. Characteristics of Research Subjects

Variable	Subject		Groups		p
	Mean ± SD	Median (min – max)	Control	Treatment	
Age (year)	50,33 ± 11,53	48 (27 – 77)	52,54 ± 10,80	48,13 ± 12,03	0,187§
Weight (kg)	61,54 ± 12,89	60,5 (40 – 98)	61,29 ± 11,59	61,79 ± 14,31	1,000‡
Height (cm)	1,57 ± 0,07	1,57 (1,44 – 1,70)	1,58 ± 0,07	1,56 ± 0,07	0,348§
Body Mass Index (kg/m^2)	24,89 ± 4,56	24,10 (17,58 – 35,63)	24,59 ± 4,66	25,19 ± 4,55	0,657§
Surgery duration (minute)	91,93 ± 50,60	96,43 (13,95 – 226,2)	72,83 ± 46,58	111,04 ± 47,96	0,019‡*
Mean Arterial Pressure (mmHg)	86,23 ± 9,32	84,67 (70,33 – 106,33)	85,56 ± 10,91	86,90 ± 7,59	0,622§
Fentanyl consumption (mg)	90,83 ± 19,98	100 (50 – 150)	88,75 ± 20,71	92,92 ± 19,44	0,980‡

Description : * Significant (P < 0,05); § Independent t-test; ‡ Mann Whitney

The mean age in the control group was 52.54 ± 10.80 while in the treatment group it was 48.13 ± 12.03. The mean body weight in the control group was 61.29 ± 11.59 while in the treatment group it was 61.79 ± 14.31. The mean height in the control group was 1.58 ± 0.07 while in the treatment group it was 1.56 ± 0.07. The mean BMI in the control group was 24.59 ± 4.66 while in the treatment group it was 25.19 ± 4.55. The mean duration of surgery in the control group was 72.83 ± 46.58 while in the treatment group it was 111.04 ± 47.96. The mean MAP in the control group was 85.56 ± 10.91 while in the treatment group it was 86.90 ± 7.59. Finally, the mean consumption of fentanyl in the control group was 88.75 ± 20.71 while in the treatment group it was 92.92 ± 19.44.

Table 2. Descriptive test results and normality of TNF-α levels in the pre-test, and the post-test and the difference

TNF-α	Groups	Mean ± SD	Median (min – max)	p£
Pre test	Control	10,00 ± 5,31	9,55 (2,90 – 24,40)	0,070*
	Treatment	11,29 ± 6,65	10,10 (2,40 – 29,80)	0,059*
Post test	Control	8,15 ± 5,31	7,00 (1,40 – 20,10)	0,058*
	Treatment	6,21 ± 5,58	5,80 (0,70 – 25,60)	0,000
Difference	Control	-1,85 ± 4,75	-,095 (-20,10 – 4,10)	0,000
	Treatment	-5,08 ± 3,70	-4,65 (-15,70 – 0,00)	0,095*

Description : TNF-α, Tumor Necrosis Factor-Alpha; * Normal distribution (P > 0,05); £ Shapiro-wilk

The results of the pairwise difference test between TNF-α pre and TNF-α post in the control group using Wilcoxon test were not significant (P=0.080) while in the treatment group the results were significant (P<0.001). In the unpaired difference test between the control group and the treatment group using Mann Whitney test, it was found that the values for TNF-α pre (P=0.461) and TNF-α post (P=0.135) were not significant, while the difference in TNF-α was significant (P=0.001).

Analysis of RPR Levels

The average RPR level before the study was 0.60 ± 0.24 and in the treatment group it was 0.57 ± 0.26. The average RPR level after the study was 0.64 ± 0.28 and in the treatment group it was 0.50 ± 0.20. The average difference in PLR levels before and after the intervention in the control group was 0.04 ± 0.10 and in the treatment group it was -0.07 ± 0.19. Normality test was done using the Shapiro-wilk test.

Table 3. Results for differences in TNF-α levels in the pre-test and the post-test and the difference

TNF-α	Groups		P
	Control (n=24)	Treatment (n=24)	
Pre test	10,00 ± 5,31	11,29 ± 6,65	0,461§
Post test	8,15 ± 5,31	6,21 ± 5,58	0,135‡
p	0,080†	<0,001¶*	
Difference	-1,85 ± 4,75	-5,08 ± 3,70	0,001‡*

Description : * Significant (P < 0,05); § Independent t; ‡ Mann Whitney; † Wilcoxon; ¶ Paired t

Table 4. Descriptive test results and normality of RPR in the pre-test and the post-test and the difference

RPR	Groups	Mean ± SD	Median (min – max)	p£
Pre test	Control	0,60 ± 0,24	0,54 (0,25 – 1,14)	0,134*
	Treatment	0,57 ± 0,26	0,49 (0,30 – 1,28)	0,000
Post test	Control	0,64 ± 0,28	0,55 (0,25 – 1,37)	0,038
	Treatment	0,50 ± 0,20	0,47 (0,23 – 1,24)	0,000
Difference	Control	0,04 ± 0,10	0,02 (-0,08 – 0,28)	0,009
	Treatment	-0,07 ± 0,19	-0,03 (-0,68 – 0,12)	0,000

Description : * Normal distribution (P > 0,05); £ Shapiro-wilk

The results of the pairwise difference test between RPR pre and RPR post in the control group and the treatment group using the Wilcoxon test were not significant (P= 0.123 and P= 0.278, respectively). In the unpaired difference test comparing the control group and the treatment group using the Mann Whitney test, it was found that the pre RPR was not significant (P=0.433) while the post RPR value (P=0.031) and the RPR difference (P=0.037) were significant.

Relationship between Operation Duration and Difference in RPR and TNF-α

Spearman's correlation test between operation duration and the difference in RPR and TNF-α resulted in a P-value of >0.05 (P = 0,911 for TNF-α and P = 0,101 for RPR), so it could be concluded that there was no significant relationship.

Table 5. Test results for differences in RPR

RPR	Groups		p
	Control (n=24)	Treatment (n=24)	
Pre test	0,60 ± 0,24	0,57 ± 0,26	0,433‡
Post test	0,64 ± 0,28	0,50 ± 0,20	0,031‡*
p	0,123†	0,278†	
Difference	0,04 ± 0,10	-0,07 ± 0,19	0,037‡*

Description: * Significant (P < 0,05); ‡ Mann Whitney; † Wilcoxon; ¶ Paired t

DISCUSSION

TNF-α (Tumor Necrosis Factor-α)

TNF-α is considered as a key regulator of proinflammatory cytokine production. TNF-α plays a significant role in increasing lipid signal transduction

mediators such as prostaglandins and platelet activating factor. TNF-α is released after tissue damage by immune cells (macrophages, lymphocytes, and mast cells) and non-immune cells (endothelial cells and fibroblasts), which plays an important role in defense mechanisms, wound healing, and post-traumatic pain.[14]

Table 6. Relationship between Surgery Duration and Difference in RPR and TNF-α

Variable	Surgery duration	
	p	r
TNF-α difference	0,911	-0,017
RPR difference	0,101	0,240

In relation to breast cancer, TNF-α is a molecule of inflammatory response, cell organization and innate immunity, participating in the pathogenesis of breast cancer. TNF-α correlates with increased tumor cell proliferation, higher malignancy grade, increased occurrence of metastases and a poor general prognosis for patients. High levels of TNF-α have been associated with high breast cancer recurrence rates.[15,16]

In this study, postoperative TNF-α levels were higher in the group with GA compared with PECS block. The difference was found higher in the PECS block group. The results are different when compared with the research of Vosoughian *et al.* who found that there was a significant increase in cytokine levels, IL-6 and TNF-α after cesarean section surgery compared to the levels before the surgery. The increase in cytokine levels was found to be higher in the group with GA than SA, where postoperative TNF-α levels were also found higher in the GA group.[17] The difference between this study and the study conducted by Vosoughian *et al.* lies in the type of disease assessed. In this study, the subjects were breast cancer patients, where there were much higher levels of pro-inflammatory cytokines when the tumor cells were still in the body. Anti-inflammatory effects of local anesthetia may have led to different findings compared to the results in our study, where these effects were found to be important in modulating the release of cytokines following regional anesthesia.

The results of this study are consistent with the results reported in some previous research. Inoue *et al.* recently conducted an in vivo study, reporting that GA combined with SA can reduce the total number of circulating tumor cells and decrease the stress response to surgery with reduced serum levels of TNF-α compared with GA alone in a mouse model of prostate cancer. Geng *et al.* reported that the combination of pectoral nerve block and stellate ganglion block effectively blunted the perioperative inflammatory response by decreasing serum TNF-α levels, reduced acute postoperative pain, stabilized perioperative hemodynamics, and provided better postoperative sleep quality compared with pectoral nerve block alone in breast cancer patients undergoing modified radical mastectomy.[18] As with previous studies, we found that anesthesia techniques contributes to TNF-α levels, and that breast cancer patients would benefit from having combination anesthesia (GA and SA). Lower levels of TNF-α indicate lower proliferation rates of cancer cells, which reduce malignancy rates and the occurrence of metastases, giving better general prognosis for patients.

RPR (Red Cell Distribution Width to Platelet Ratio)

RPR is obtained from comparing the ratio of RDW to the number of platelets. RDW is an inflammatory marker and a prognostic marker for various diseases including malignancies. RDW and RPR as inflammatory, recurrence, and prognostic markers in breast cancer have not been widely studied.[19]

In research comparing the RDW and RPR ratios before and after therapy for breast cancer, it was stated that the higher the levels of both, the worse the patient's survival would be. In the microenvironment surrounding cancer, the inflammation that occurs increases tumor growth, invasion, angiogenesis, and cancer metastasis. Although the mechanism underlying the relationship between RDW and survival or disease activity is not yet known, an increase in RDW is thought to be due to ongoing inflammation which increases oxidative stress and then disrupts the erythropoiesis process. During inflammation, rapid red blood cell maturation disrupts the red blood cell membrane. Increased metabolism and blood cell activity, especially with the formation of new vessels or the occurrence of metastases, increases the distribution of erythrocytes.[20–22]

In this study, the decrease in RPR in the treatment group was not significant, but there were significant differences in RPR between the control group compared to the treatment group. An increase in postoperative RPR levels in the control group was observed in this study. These results can be related to other factors that increase the occurrence of an inflammatory process, such as the use of mechanical ventilation, use of opioid drugs, or surgical treatment, which are not included in this research. On the other hand, RPR levels in the patients in the treatment group were lowered. This finding suggests that anesthesia technique contributes to the expression of inflammatory levels. To reduce the levels of RPR in the treatment group, giving combination anesthesia (GA and SA) would benefit breast cancer patients

after surgery. Lower levels of RPR showed reduced cancer cells growth and reduced inflammation.

Previous studies have shown that RPR is a good marker for detecting the presence of inflammation around tumors, but it isa poor prognostic factor for patients with HR+ lung, colon, kidney and breast cancer. The reason is not yet known for certain, but an imbalance between the two RDW and platelet values can lead to a poor prognosis for recurrence and patient survival.

Previous studies have reported similar findings to the results of this study in that there were no significant differences in RDW and RPR before treatment, but significant differences after treatment in relation to survival. RPR may be a reliable prognostic indicator in breast cancer, although there have been no reports regarding this. This mechanism is linked to various circulating inflammatory cytokines that affect the presence of red blood cells and nutritional status that plays a role in hematopoiesis. Nutritional status refers to a deficiency of raw materials for red blood cell production (Fe, B12, and folic acid) that is associated with reduced body weight and appetite in people with cancer. However, this study did not examine those risk factors.[22–24]

Anesthesia Technique and Operation Duration with RPR and TNF-α Difference

Differences in anesthesia techniques and duration of surgery provide different effects on the patient's immune system. Immunosuppression is a common occurrence in surgery, where the operation creates a wound due to intentional tissue damage and involves the healing process. A decrease in the number of T lymphocytes causes a change in the balance between regulatory T cells and helper T cells. This reduces the number of NK cells and increases the number of neutrophils. Another study comparing general and regional anesthesia in hip surgery showed that different anesthetic methods influence cytokine responses. Cytokines assessed in the form of IL-1beta, TNF-α, IL-6 were found to increase in TNF-α and IL-6 slightly higher after surgery in the regional anesthesia group compared to the general anesthesia group, although this finding was not statistically significant.[10,25]

Limitations

This study did not take into account any potential confounders that could influence TNF-α and RPR levels, namely age, BMI, patient's comorbidities, use of medication, depth of anesthetic, and duration of surgery. In addition, the use of medications and other underlying diseases of patients, which affect immunosuppressants, were not taken into account in our study. Apart from that, there are still many factors and other biomarkers released in state of inflammatory that may play a role in invasion, proliferation and metastasis in breast cancer.

CONCLUSION

The results of this study showed that inflammatory biomarkers, in the form of TNF-α and the distribution width ratio of red blood cells to platelets (RPR) in breast cancer surgery were found to be lower in the combination of PECS block II with general anesthesia than in general anesthesia only.

ETHICAL CONSIDERATIONS

This research has received ethical clearance from the Health Research Ethics Commission of Dr. Kariadi Hospital, Semarang with No. 1548/EC/KEPK-RSDK/2023.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

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REFERENCES

1. Manuaba TW. 2010. Panduan Penatalaksanaan Kanker Solid PERABOI. Jakarta, Sagung Seto.
2. Alkabban FM, Ferguson T. Breast Cancer. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482286/
3. Desborough JP: The stress response to trauma and surgery. *Br J Anaesth*. 2000;85(1):109–17 10.1093/bja/85.1.109. doi: 10.1093/bja/85.1.109.
4. Allen MD, Jones LJ. The role of inflammation in progression of breast cancer: friend or foe?(Review). *Int J Oncol*. 2015;47(3):797-805. doi: 10.3892/ijo.2015.3075.
5. Warwick R, Mediratta N, Shackcloth M, Shaw M, McShane J, Poullis M. Preoperative red cell distribution width in patients

undergoing pulmonary resections for non-small-cell lung cancer. *Eur J Cardiothorac Surg*. 2014;45(1): 108-13. doi: 10.1093/ejcts/ezt275.
6. Bozkurt G, Korkut AY, Soytaş P, Dizdar SK, Erol ZN. The role of red cell distribution width in the locoregional recurrence of laryngeal cancer. *Braz J Otorhinolaryngol*. 2019;85(3):357–64. doi: 10.1016/j.bjorl.2018.03.004.
7. Hsing CH, Wang JJ. Clinical implication of perioperative inflammatory cytokine alteration. *Acta Anaesthesiol Taiwanica*. 2015;53(1):23–8. doi: 10.1016/j.aat.2015.03.002.
8. Wall T, Sherwin A, Ma D, Buggy DJ. Influence of perioperative anaesthetic and analgesic interventions on oncological outcomes: a narrative review. *Br J Anaesth*. 2019;123(2):135–50. doi: 10.1016/j.bja.2019.04.062.
9. Bashandy GMN, Abbas DN. Pectoral nerves I and II blocks in multimodal analgesia for breast cancer surgery: a randomized clinical trial. *Reg Anesth Pain Med*. 2015;40(1):68–74.
10. Cui X, Zhu C, Chen P, Qu M, Zhang B, Li H. Effect of pectoral nerve block type II under general anesthesia on the immune function of patients with breast cancer. *Am J Surg*. 2020;220(4):938–44. doi:10.1016/j.amjsurg.2020.03.008.
11. Yoon JY, Kwak MS, Kim HI, Cha JM. Seasonal variations in the diagnosis of the top 10 cancers in Korea: A nationwide population-based study using a common data model. *Journal of gastroenterology and hepatology*, 2021:36(12), 3371–3380. h. doi: 10.1111/jgh.15634.
12. Holmberg L, Adolfsson J, Mucci L, Garmo H, Adami HO, Möller H, et al. Season of diagnosis and prognosis in breast and prostate cancer. Cancer causes & control : CCC, 2009:20(5), 663–670. doi:10.1007/s.
13. Doyle DJ, Hendrix JM, Garmon EH. American Society of Anesthesiologists Classification. *StatPearls Treasure Island (FL): StatPearls Publishing*; 2023 Jan-. doi: 10.1007/s10552-008-9279-6.
14. Parameswaran N, Patial S. Tumor Necrosis Factor-α Signaling in Macrophages. *Crit Rev Eukaryot Gene Expr*. 2010;20(2):87. doi: 10.1615/critreveukargeneexpr.v20.i2.10.
15. An L, Dou X, Wang M, Luo W, Ma Q, Liu X. Involvement of TNF-alpha and IL-10 in breast cancer and patient survival. *Trop J Pharm Res*. 2020;19(10):2033–9. doi: 10.4314/tjpr.v19i10.2.
16. Liu W, Lu X, Shi P, Yang G, Zhou Z, Li W, et al. TNF-α increases breast cancer stem-like cells through up-regulating TAZ expression via the non-canonical NF-κB pathway. *Sci Reports* 2020 101. 2020 Feb;10(1):1–11. doi: 10.1038/s41598-020-58642-y.
17. Vosoughian M, Dahi M, Dabir S, Moshari M, Tabashi S, Mosavi Z. Effects of General Anesthesia Versus Spinal Anesthesia on Serum Cytokine Release After Cesarean Section: A Randomized Clinical Trial. *Anesthesiol Pain Med* 2021 112. 2021 Apr;11(2):111272. doi: 10.5812/aapm.111272.
18. Tseng WC, Lai HC, Huang YH, Chan SM, Wu ZF. Tumor Necrosis Factor Alpha: Implications of Anesthesia on Cancers. *Cancers (Basel)*. 2023 Feb;15(3). doi: 10.3390/cancers15030739.
19. Takeuchi H, Abe M, Takumi Y, Hashimoto T, Miyawaki M, Okamoto T, et al. Elevated red cell distribution width to platelet count ratio predicts poor prognosis in patients with breast cancer. *Scientific reports*, 9(1), 3033. doi: 10.1038/s41598-019-40024-8.
20. Wang PF, Song SY, Guo H, Wang TJ, Liu N, Yan CX. Prognostic role of pretreatment red blood cell distribution width in patients with cancer: A meta-analysis of 49 studies. *J Cancer*. 2019;10(18):4305–17. doi: 10.7150/jca.31598.
21. Takeuchi H, Abe M, Takumi Y, Hashimoto T, Miyawaki M, Okamoto T, et al. Elevated red cell distribution width to platelet count ratio predicts poor prognosis in patients with breast cancer. *Sci Rep*. 2019;9(1):1–7. doi: 10.1038/s41598-019-40024-8.
22. Lee HS, Jung EJ, Kim JM, Kim JY, Kim JR, Kim TH, et al. The usefulness of red blood cell distribution width and its ratio with platelet count in breast cancer after surgery and adjuvant treatment: a retrospective study. *Gland Surg*. 2022;11(12):1864–73. doi: 10.21037/gs-22-410.
23. Goyal H, Gupta S, Singla U. Level of red cell distribution width is affected by various factors. *Clinical chemistry and laboratory medicine*, 2016:54(12), e387. doi:10.1515/cclm-2016-0195.
24. Karachaliou N, Pilotto S, Bria E, Rosell R. Platelets and their role in cancer evolution and immune system. *Translational lung cancer research*, 2015:4(6), 713–720. doi:10.3978/j.issn.2218-6751.2015.10.09.

25. Høgevold HE, Lyberg T, Kähler H, Haug E, Reikerås O. Changes in plasma IL-1beta, TNF-alpha and IL-6 after total hip replacement surgery in general or regional anaesthesia. *Cytokine*, 2000:12(7), 1156–1159. doi:10.1006/cyto.2000.

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