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# Impact of Anesthesia Method on Immune Response in Patients Undergoing Radical Surgery for Breast Cancer (a Meta-Analysis of Comparative Clinical Studies)

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# Влияние выбора метода анестезии на иммунный ответ пациенток, перенесших радикальную операцию по поводу рака молочной железы (мета-анализ сравнительных клинических исследований)

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## Summary

**Introduction and aim.** Recent evidence suggests that inhalation anesthesia (IA) is associated with higher cancer mortality than total intravenous anesthesia (TIVA), possibly due to a modulation of the immune response.

**The aim of this study** was to determine the impact of anesthesia techniques on selected parameters of patient immunity considering the evidence of relationship between the anesthesia methods and immune status and, consequently, the incidence of cancer recurrence.

**Methods.** We performed a meta-analysis of clinical studies published in PubMed, Google Scholar, and Cochrane databases, aimed at assessing the impact of anesthesia on the postoperative immune status of patients undergoing breast cancer (BC) surgery. Five randomized and three observational studies were included (a total of 637 patients, of which 320 (50.2%) in the TIVA group). Data on leukocyte counts, matrix metalloproteinases (MMP) 9 and 3, interleukins (IL) 6 and 10 levels, and neutrophil-lymphocyte index (NLI) values were retrieved.

**Results.** Patients after breast cancer surgery who underwent TIVA had significantly lower white blood cell counts (standardized mean difference (SMD)=–0.32; 95% CI: –0.58 to –0.06; $I^2$=58%, $P$=0.020) and MMP-9 (SMD=–0.35; 95% CI: –0.67 to –0.03; $P$=0.030; $I^2$=0%) in the postoperative period compared with patients re-

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ceiving IA. No significant differences in the levels of MMP-3, IL-6, IL-10, and NLI values were found between the two groups.

**Conclusion.** The patients who underwent breast cancer surgery under TIVA had lower blood leukocyte counts and levels of MMP-9, which is involved in the remodeling of extracellular matrix, compared with those operated on under IA, suggesting that the anesthesia method may have an impact on the immunity of breast cancer patients.

***Keywords: anesthesia; breast cancer; surgery; immunomodulation; inhaled anesthesia; intravenous anesthesia***

**Conflict of interest.** The authors declare no conflict of interest.

**The full text version of the paper is available at www.reanimatology.com**

## Introduction

Radical surgery remains the most effective and widely used method of treatment of solid tumors. It is recommended for at least 80% of newly diagnosed cancer patients [3]. Moreover, recent tendency points to a highly probable rise of this parameter, at least for the foreseeable future [3]. For example, the need for surgical treatment of breast cancer (BC) worldwide will increase from 3,022,883 operations in 2015 to 3,810,168 operations in 2030 [3].

Most surgical interventions for malignant tumors have been performed under general anesthesia, and most studies in the area of intraoperative protection have been limited to the study of anesthesia parameters in different types of surgeries. Today, however, new data appear indicating that the use of inhalational anesthesia (IA) may be associated with a greater frequency of adverse outcomes in the long term after radical operations, which, in turn, can be explained by allegedly higher frequency of tumor recurrence [4]. Halogenated anesthetics are considered to contribute to the initiation of tumor regrowth due to impact on cell apoptosis, systemic inflammatory response, and immunosuppression [5-8]. Thus, the immune system seems to be the main link underlying the possible negative effect of anesthesia on postoperative survival rate in cancer patients. This elegant hypothesis, however, has not yet been sufficiently confirmed by the results of evidence-based studies [9]. Perhaps one of the significant limitations of previous meta-analyses was the attempt of bringing together heterogeneous groups of patients with various stages of cancer, major differences in the extent and area of surgery, as well as different levels of baseline mortality within a single study.

Therefore, the aim of this systematic review was to determine the impact of anesthesia method (TIVA vs. IA) on the serum levels of proinflammatory cytokines and matrix metalloproteinases in patients who underwent surgery for breast cancer.

## Material and Methods

This meta-analysis follows the guidance outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10-13] and is registered in PROSPERO (CRD42021255272).

**The strategy for study search and selection.** Two independent investigators (M. Ya. and K. K.) performed a search in PubMed, Cochrane, and Google Scholar databases for articles published in the past 10 years. The meta-analysis included randomized controlled trials published in peer-reviewed journals, prospective and retrospective cohort studies comparing the effects of IA and TIVA on the immunity of breast cancer patients. Experimental animal studies, studies with insufficient information for performing meta-analysis (e.g., lacking absolute values of quantitative parameters) were excluded. After elimination of duplicates, two reviewers selected publications suitable for full-text analysis to decide on inclusion/non-inclusion according to predetermined criteria. The final decision was made by consensus, if there was a discrepancy, by the Principal Investigator. Searches were conducted in the form of queries using the following keywords: [anesthesia breast cancer / total intravenous anesthesia versus volatile anesthetics breast cancer / TIVA inhalation anesthesia breast cancer / breast cancer propofol / neutrophil-lymphocyte ratio breast cancer anesthesia / anesthesia immune cell / anesthesia immune response]. In addition, the review of literature sources in the analyzed papers was used.

A flowchart of the paper selection is presented in Fig. 1. Of the 1861 publications initially identified in the databases, only five randomized and three non-randomized studies met the inclusion/exclusion criteria (637 patients: 320 in the TIVA group and 317 in the IA group) and were analyzed.

**Data collection.** The following data were retrieved from each study: design, method of anesthesia (IA or TIVA), quantitative immune parameters (measured by the authors of each original study).

**Statistical analysis.** Data were analyzed using the RevMan v.5.3 tool (Nordic Cochrane Center, Cochrane Collaboration).

When the authors presented the data as median (interquartile range) or mean (confidence interval), the recommended conversion methods of «mean ± standard deviation» were applied [14, 15]. Heterogeneity of the studies was assessed using the I2 heterogeneity coefficient and the Cochrane coefficient Q. Continuous data were compared using standardized mean difference (SMD) and its 95% confidence interval (CI). Two models (fixed and random effects ones) were used to summarize the magnitude of the standardized difference in mean values [16]. The random effects model was used if moderate to high heterogeneity (defined as $I^2$>60%) was present.

The primary endpoint of the study was the neutrophil-lymphocyte ratio (NLR) on day 1 post-surgery.

Secondary endpoints were the leukocyte count and the levels of IL-6, IL-10, MMP-3, MMP-9 at the above-mentioned time points.

**Assessing the risk of systematic bias.** Appropriate Cochrane tools for randomized (RoB 2) [17] and non-randomized studies (ROBINS-I) [18] were used to assess the risk of systematic bias. Papers included in the meta-analysis were independently assessed for the risk of bias by two reviewers (K. K. and M. Ya.) and reviewed by the third (L. B.). Two statistical tests, the Egger [19] and Begg test (MedCalc Statistical Software, version 19.5.6) [20] were used to assess the risk of bias in the publication. Funnel plots were used for visual assessment of publication bias [21].

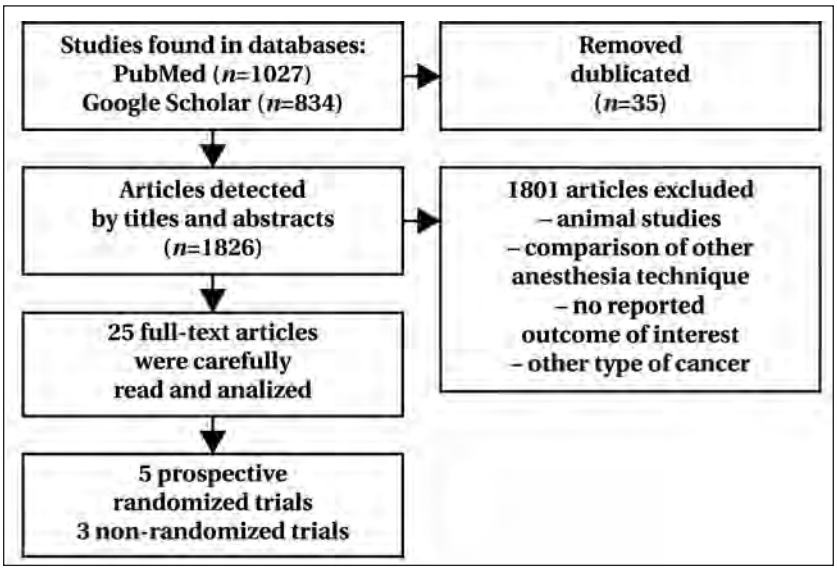



**Fig. 1. Flowchart of study selection for the meta-analysis.**

## Results

**Study characteristics.** The characteristics of the studies included in the paper are presented in the table.

**Data analysis.** No significant intergroup differences were found for the primary endpoint (Fig. 2, *a*): the mean NLR in the TIVA group was 2.45±1.32 versus 2.74±1.72 in the IA group (SMD=–0.25; 95% CI: –0.65 to 0.17; *P*=0.240, $I^2$=71%; three studies included).

Figure 2, *b* shows the results of 4 studies comparing the leukocyte counts in the postoperative

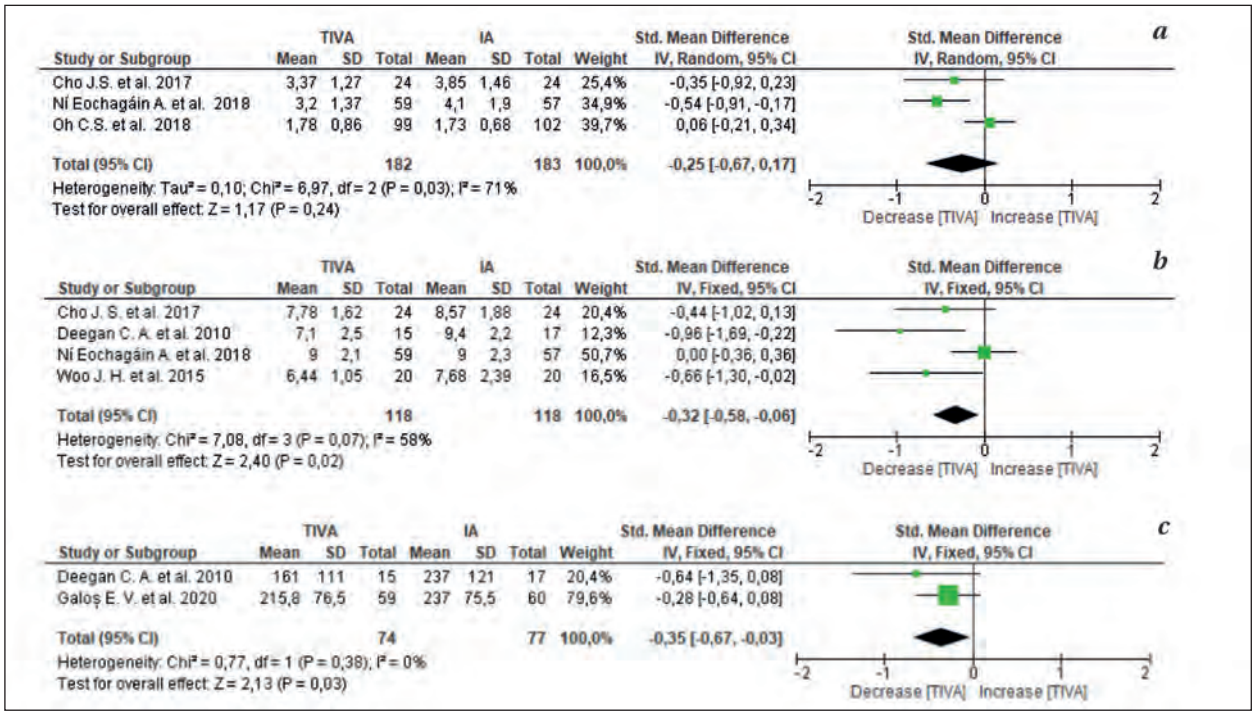



**Fig. 2. A meta-analysis of postoperative neutrophil-leucocyte ratio (*a*), leucocyte count (*b*), and MMP-9 level (*c*) in breast cancer patients with inhaled anesthesia (IA) and total intravenous anesthesia (TIVA) (forest plot diagram).**
**Note.** The graphs show study, mean and standard deviation (SD), sample size, study weight, standardized mean difference (SMD), its 95% confidence interval (CI), and estimated heterogeneity and overall effect (*P*-value). The square figure shown for each study represents SMD for the corresponding study and the accompanying horizontal line shows its 95% CI. The diamond-shaped figure represents the pooled SMD for all studies, its horizontal part, 95% CI. The square figures of different sizes indicate the weight of single studies in the overall analysis with respect to sample size and effect size.

period in patients from the TIVA and IA groups. Patients in the TIVA group had significantly lower leukocyte counts compared with patients who received volatile anesthetics (mean leukocyte count in the TIVA group=8.08±2.16–103/ml versus 8.75±2.26–103/ml in the IA group, SMD=–0.32; 95% CI: –0.58 to –0.06; *P*=0.020; $I^2$=58%) (Fig. 2, *b*). Visual inspection of the funnel plot (supplementary Fig. 1) as well as the Egger (*P*=0.005) and Begg (*P*=0.042) tests suggest the presence of publication bias.

Postoperative levels of matrix metalloproteinase-9 were evaluated in two studies. Patients who received total intravenous anesthesia had significantly lower MMP-9 levels in the postoperative period compared with patients from the IA group (mean MMP-9 value in the TIVA group=204.7±86.6 ng/mL versus 237.0±84.8 ng/mL in the IA group; SMD=–0.35; 95% CI: –0.67 to –0.03; *P*=0.030; $I^2$=0%) (Fig. 2, *c*).

No significant differences were found in serum levels of the following cytokines:

- IL-6 (mean value of IL-6 in the TIVA group was 215.8±170.5 pg/mL versus 232.8±148.4 pg/mL in the IA group; SMD=–0.34; 95% CI: –0.82 to 0.33; *P*=0.404; $I^2$=77%; four studies included) (supplemental Fig. 2, *a*),
- IL-10 (mean IL-10 in the TIVA group, 789.9±714.7 pg/mL versus 723.4±470.0 pg/mL in the IA group; SMD=0.16; 95% CI: –0.08 to 0.40; *P*=0.190; $I^2$=10%; three studies included) (supplemental Fig. 2, *b*)

as well as MMP-3 (mean MMP-3 in TIVA group=341.4±697.1 ng/mL versus 507.3±1120.4 ng/mL in IA group; SMD=–0.10; 95% CI: –0.99 to 0.80; *P*=0.830; $I^2$=80%; two studies included) (supplemental Fig. 2, c).

**The systematic bias risk.** The results of the systematic error risk analysis are presented in supplemental Fig. 3.

Overall, the two randomized controlled trials had a low risk of systematic error, while all of the observational studies were characterized by a critical risk of such error.

**Table. Characteristics of the included studies (original data are presented).**

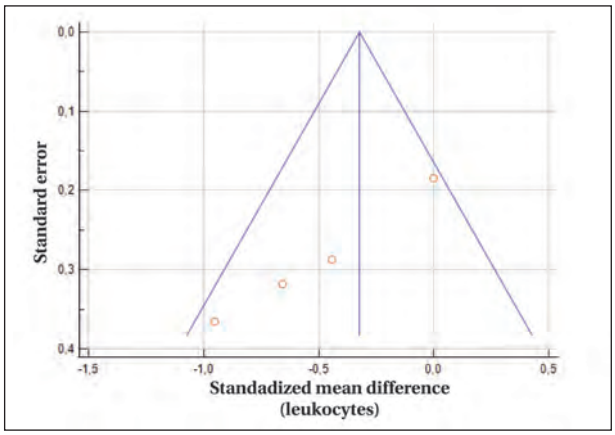
| Study and sample size (*n*) | Design | Leucocytes, $10^3$/мл | IL-6, pg/ml | IL-10, pg/ml | MMP-3, ng/ml | MMP-9, ng/ml | Neutrophil-lymphocyte ratio |
|---|---|---|---|---|---|---|---|
| Kim R. et al. 2017,<br>TIVA *n*=21<br>IA *n*=16 | Prospective non-randomized [22] | — | Median and quartiles<br>TIVA: 4.1 [3.2; 8.7]<br>IA: 15.4 [9.6; 23.9] | — | — | — | — |
| Deegan C. A. et al. 2010,<br>TIVA *n*=15<br>IA *n*=17 | Randomized [23] | Mean and 95% CI<br>TIVA: 7.1 (6.2–8.0)<br>IA: 9.4 (8.6–10.2) | Median and quartiles<br>TIVA: 9.3 [5.5; 19.8]<br>IA: 8.3 [4.4; 11.1] | Median and quartiles<br>TIVA: 2358 [1652; 3245]<br>IA: 1528 [1406; 2344] | Median and quartiles<br>TIVA: 1693 [1361; 1918]<br>IA: 2110 [1562; 3166] | Median and quartiles<br>TIVA: 123 [112; 248]<br>IA: 264 [148; 298] | — |
| Cho J. S. et al. 2017,<br>TIVA *n*=24<br>IA *n*=24 | Randomized [24] | Mean ± standard deviation<br>TIVA: 7.78±1.62<br>IA: 8.57±1.88 | — | — | — | — | Mean ± standard deviation<br>TIVA: 3.37±1.27<br>IA: 3.85±1.46 |
| Ní Eochagáin A. et al. 2018,<br>TIVA *n*=59<br>IA *n*=57 | Randomized [25] | Median and quartiles<br>TIVA: 9.0 (IQR=2.8)<br>IA: 9.0 (IQR=3.1) | — | — | — | — | Median and quartiles<br>TIVA: 3.0 [2.4; 4.2]<br>IA: 4 [2.9; 5.4] |
| Oh C. S. et al. 2018,<br>TIVA *n*=99<br>IA *n*=102 | Randomized [26] | — | Median and quartiles<br>TIVA: 330 [230; 400]<br>IA: 340 [290; 370] | Median and quartiles<br>TIVA: 610 [500; 730]<br>IA: 610 [530; 670] | — | — | Median and quartiles<br>TIVA: 1.62 [1.29; 2.43]<br>IA: 1.68 [1.3; 2.21] |
| Lim J. A. et al. 2018,<br>TIVA *n*=23<br>IA *n*=21 | Randomized [27] | — | Median and quartiles<br>TIVA: 90 [90; 100]<br>IA: 90 [90; 100] | Median and quartiles<br>TIVA: 470 [430; 570]<br>IA: 470 [440; 500] | — | — | — |
| Woo J. H. et al. 2015,<br>TIVA *n*=20<br>IA *n*=20 | Prospective case-control [28] | Median and quartiles<br>TIVA: 6.92 [5.54; 6.86]<br>IA: 7.62 [6.22; 9.21] | — | — | — | — | — |
| Galoș E. V. et al. 2020,<br>TIVA *n*=59<br>IA*n*= 60 | Randomized [29] | — | — | — | Mean ± standard deviation<br>TIVA: 6.90±5.76<br>IA: 5.30±4.42 | Mean ± standard deviation<br>TIVA: 215.8±76.5<br>IA: 237.0±75.5 | — |

## Discussion

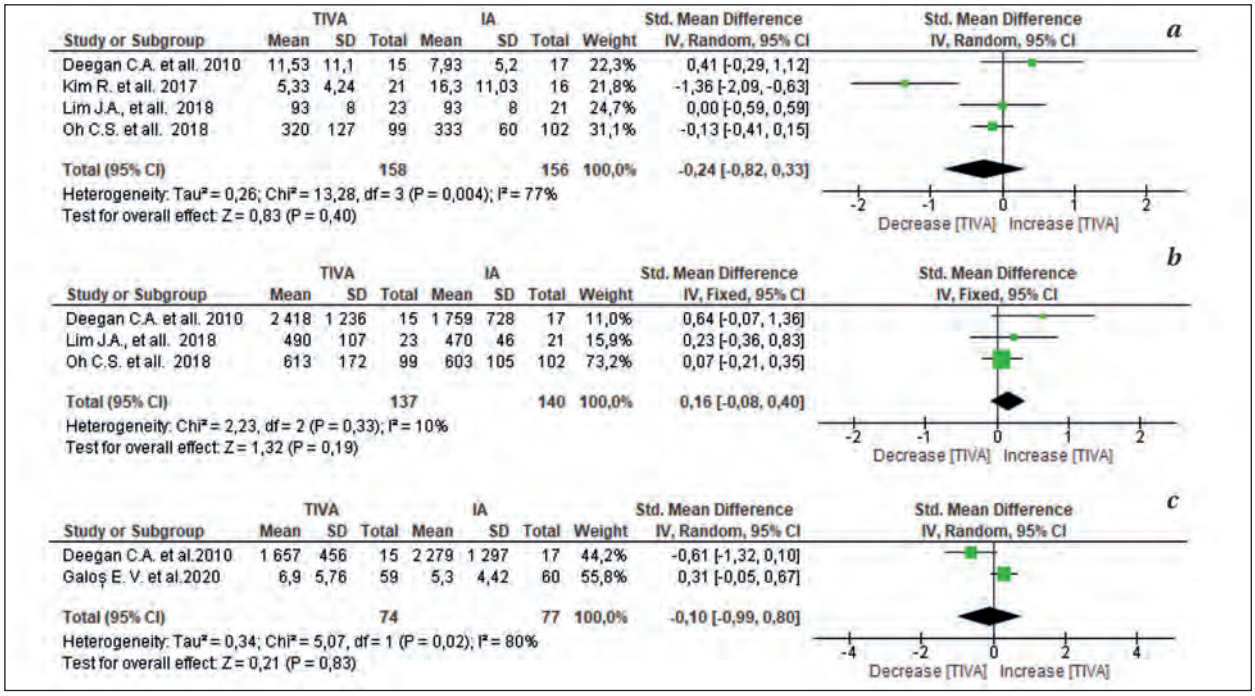
The present study found no differences in postoperative NLR levels in the compared groups. Given the high risk of systematic error in baseline observational studies, the lack of difference in the primary endpoint can be interpreted as a questionable result. We can neither confirm nor deny the effect of inhalation anesthesia on the immune status of patients who have undergone radical surgery for breast cancer. This situation is very similar to the one observed with the study of the effect of inhalation anesthesia on the immune status and mortality in cancer patients in general: some researchers confirm such effect [30, 31], others fail to demonstrate it [9, 32]. Meanwhile, the results of meta-analysis do not provide a definitive answer [33, 34]. Perhaps we should wait for the results of large RCTs, which are currently underway (NCT01975064, NCT04316013) and close to completion.

The observed intergroup difference in leukocyte counts can hardly be interpreted in favor of one or another anesthesia method, because this parameter in both groups hardly exceeds the reference values. This observation only confirms the hypothesis formulated in the previous paragraph.

However, higher postoperative MMP-9 levels were observed in patients with breast cancer who underwent surgery under IA. In an experimental study, Leifler et al. [35] showed that MMP-9 is in-




**Supplemental Fig. 1. The risk of publication bias for studies evaluating the post-surgery leucocyte count (funnel-plot diagram).**
**Note.** The graph shows the results of the tests (X-axis) and accuracy (Y-axis). In the figure above, the results are presented as standardized mean difference (SMD) and the accuracy is the standard error of the SMD. Each point on the graph represents a different study. Two lines on each side representing the 95% confidence intervals are also shown. The middle solid line indicates the overall effect of the meta-analysis. A perfect funnel plot is one where the included studies are symmetrically scattered on either side of the overall effect line. In the figure shown, there is a leftward skew, indicating publication bias.

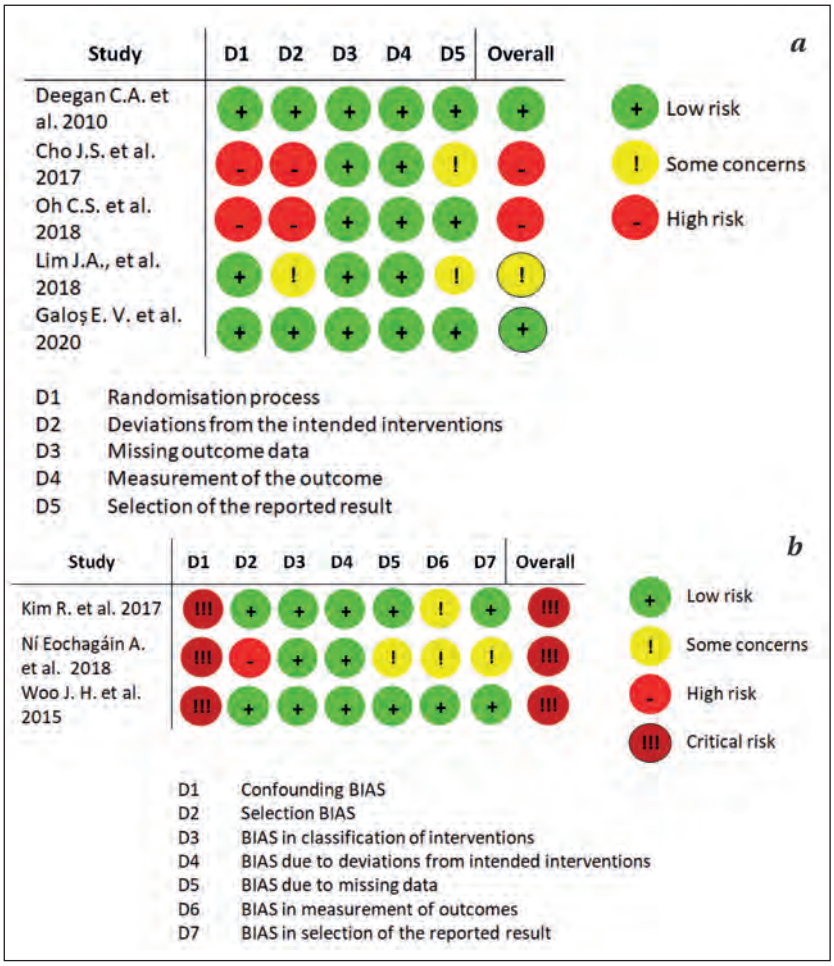



**Supplemental fig. 2. A meta-analysis of postoperative serum IL-6 (*a*), IL-10 (*b*), and MMP-9 level (*c*) in breast cancer patients with inhaled anesthesia (IA) and total intravenous anesthesia (TIVA) (forest plot diagram).**
**Note.** The graphs show study, mean and standard deviation (SD), sample size, study weight, standardized mean difference (SMD), its 95% confidence interval (CI), and estimated heterogeneity and overall effect (*P*-value). The square figure shown for each study represents SMD for the corresponding study and the accompanying horizontal line shows its 95% CI. The diamond-shaped figure represents the pooled SMD for all studies, its horizontal part, 95% CI. The square figures of different sizes indicate the weight of single studies in the overall analysis with respect to sample size and effect size.

volved in the regulation of antitumor innate immune responses, thus influencing the metastatic activity of malignant neoplasms. The undoubted importance of MMP-9 expression level as a prognostic marker of survival in breast cancer was also confirmed in a large meta-analysis including 15 studies (from 2001 to 2012) with 2344 participants. This meta-analysis showed that positive MMP-9 expression was associated with lower overall survival (adjusted hazard ratio (HR): 1.70, 95% CI: 1.41–2.04) and recurrence-free survival (adjusted HR: 1.54, 95% CI: 1.17–2.01) in BC patients [36]. More recently, Ren et al. performed a meta-analysis of 28 studies involving 4,944 patients (including 9 MMP-9 studies, *N*=1,044), confirming the negative effect of increased MMP-9 expression on overall survival (relative risk (RR)=1.694, 95% CI: 1.347–2.129, *P*<0.001; HR=1.611, 95% CI: 1.419–1.830, *P*<0.001) [37].

Thus, the differences in MP-9 levels in the compared groups observed in this study do not allow us to dismiss the possible effect of IA on the immune status of patients with breast cancer and confirm the limited knowledge of the problem under discussion.

We did not evaluate the impact of the compared methods of anesthesia on the levels of IL-6, IL-10, and MMP-3, which may argue against the hypothesis of a negative effect of IA on the systemic inflammatory response and immunity, in general.




**Supplemental fig. 3. Risk assessment of bias in randomized trials using the ROB-2 tool (*a*) and in non-randomized trials using the ROBINS-I tool (*b*).**
**Note.** The figure illustrates the distribution of risk estimates of bias for randomized (*a*) and non-randomized (*b*) trials across individual domains that could potentially affect the study quality. In (*a*) the success and adequacy of randomization process (D1), the presence of potential differences in patient management between groups (D2), possible missing data (D3), the objectivity and standardization of endpoint assessment in the study groups (D4), and possible selective presentation of results (D5) are assessed. In (*b*), the impact of confounding factors potentially affecting the study endpoint (D1), bias in study patient selection (D2), possible bias in classifying interventions (D3) and bias in assigning patients to certain interventions in various groups (D4), missed data (D5), non-standardized and biased assessment of endpoints in the study groups (D6), and selective presentation of results (DR7) are assessed.

Thus, contradictory data have been obtained that make it difficult to unambiguously evaluate the impact of anesthesia method on the immune status of patients after radical surgery for breast cancer.

**Limitations.** A marked heterogeneity of data was found while pooling of IL-6 levels and NLR scores from various studies in the meta-analysis, which may have affected the significance of the results.

Only 3 of the 8 studies included in the meta-analysis had a «low» or «moderate» risk of systematic bias, which limits the clinical significance of the results and necessitates a multicenter RCT to evaluate the impact of anesthesia on the immune parameters of patients with BC.

In addition, the results come from single-center RCTs, which are known to overestimate the effect size of an intervention compared to the multicenter ones [38, 39].

Nevertheless, a large multicenter RCT for a comprehensive evaluation of the impact of IA on inflammation and immune system in patients who underwent breast cancer surgery is currently needed to definitively answer the question of whether the anesthesia method affects the immune status of such patients. Only a study evaluating early postoperative complications and long-term survival will provide a rationale for using IA or avoiding this method of anesthesia for breast cancer surgery.

## Conclusion

Patients with breast cancer operated under TIVA had lower MMP-9 levels compared to those operated under IA, which could suggest that IA has a negative effect on the immune status of patients with breast cancer.

The impact of different anesthesia methods on the immune status of patients should be further investigated by measurement of classical immune parameters such as immunoglobulins, complement components, acute phase proteins (in particular, high-sensitivity C-reactive protein), cellular immunity characteristics.

## References

1. *Tsimberidou A.M., Fountzilas E., Nikanjam M., Kurzrock R.* Review of precision cancer medicine: evolution of the treatment paradigm. *Cancer Treat Rev*. 2020; 86: 102019. DOI: 10.1016/j.ctrv.2020.102019. PMID: 32251926.
2. *Zaimy M.A., Saffarzadeh N., Mohammadi A., Pourghadamyari H., Izadi P., Sarli A., Moghaddam LK., Paschepari SR., Azizi H., Torkamandi S., Tavakkoly-Bazzaz J.* New methods in the diagnosis of cancer and gene therapy of cancer based on nanoparticles. *Cancer Gene Ther*. 2017; 24 (6): 233–243. DOI: 10.1038/cgt.2017.16. PMID: 28574057.
3. *Sullivan R., Alatise O.I., Anderson B.O., Audisio R., Autier P., Aggarwal A., Balch C., Brennan M.F., Dare A., D'Cruz A., Eggermont A.M., Fleming K., Gueye S.M., Hagander L., Herrera C.A., Holmer H., Ilbawi A.M., Jarnheimer A., Ji J.F., Kingham T.P., Liberman J., Leather A.J.M., Meara J.G., Mukhopadhyay S., Murthy S.S., Omar S., Parham G.P., Pramesh C.S., Riviello R., Rodin D., Santini L., Shrikhande S.V., Shrime M., Thomas R., Tsunoda A.T., van de Velde C., Veronesi U., Vijaykumar D.K., Watters D., Wang S., Wu Y-L., Zeiton M., Purushotham A.* Global cancer surgery: delivering safe., affordable., and timely cancer surgery. *Lancet Oncol*. 2015; 16 (11): 1193–1224. DOI: 10.1016/S1470-2045 (15)00223-5. PMID: 26427363.
4. *Soltanizadeh S., Degett T.H., Gögenur I.* Outcomes of cancer surgery after inhalational and intravenous anesthesia: a systematic review. *J Clin Anesth*. 2017; 42: 19–25. DOI: 10.1016/j.jclinane.2017.08.001. PMID: 28797751.
5. *Snyder G.L., Greenberg S.* Effect of anaesthetic technique and other perioperative factors on cancer recurrence. *Br J Anaesth*. 2010; 105 (2): 106–115. DOI: 10.1093/bja/aeq164. PMID: 20627881.
6. *Adams J.M., Cory S.* The Bcl-2 apoptotic switch in cancer development and therapy. *Oncogene*. 2007; 26 (9): 1324–1337. DOI: 10.1038/sj.onc.1210220. PMID: 17322918.
7. *Jaura A.I., Flood G., Gallagher H.C., Buggy D.J.* Differential effects of serum from patients administered distinct anaesthetic techniques on apoptosis in breast cancer cells in vitro: a pilot study. *Br J Anaesth*. 2014; 113 (Suppl 1): i63–7. DOI: 10.1093/bja/aet581. PMID: 25009197.
8. *Yan T., Zhang G-H., Wang B-N., Sun L., Zheng H.* Effects of propofol/remifentanil-based total intravenous anesthesia versus sevoflurane-based inhalational anesthesia on the release of VEGF-C and TGF-β and prognosis after breast cancer surgery: a prospective, randomized and controlled study. *BMC Anesthesiol*. 2018; 18 (1): 131. DOI: 10.1186/s12871-018-0588-3. PMID: 30243294.
9. *Likhvantsev V., Yadgarov M., Di Piazza M., Kadantseva K.* Inhalation vs total intravenous anesthesia in cancer surgery: where is the «pendulum» now? (meta-analysis and review). *General Reanimatology*. 2020; 16 (6): 91–104. DOI: 10.15360/1813-9779-2020-6-91-104.
10. *Liberati A., Altman D.G., Tetzlaff J., Mulrow C., Gøtzsche P.C., Ioannidis J.P., Clarke M., Devereaux P.J., Kleijnen J., Moher D.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009; 6 (7): e1000100. DOI: 10.1371/journal. pmed.1000100. PMID: 19621070.
11. *Moher D., Liberati A., Tetzlaff J., Altman D.G., PRISMA Group.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009; 6 (7): e1000097. DOI: 10.1371/journal. pmed.1000097. PMID: 19621072.
12. *Dixon E., Hameed M., Sutherland F., Cook D.J., Doig C.* Evaluating meta-analyses in the general surgical literature: a critical appraisal. *Ann Surg*. 2005; 241 (3): 450–459. DOI: 10.1097/01.sla.0000154258. 30305.df. PMID: 15729067.
13. *Young C., Horton R.* Putting clinical trials into context. *Lancet*. 2005; 366 (9480): 107–108. DOI: 10.1016/S0140-6736 (05)66846-8. PMID: 16005318
14. *Higgins J. P.T., Thomas J., Chandler J., Cumpston M., Li T., Page M. J., Welch V.A.* (eds.). Cochrane handbook for systematic reviews of interventions. 2nd Edition. Chichester (UK). John Wiley & Sons; 2019: 1–694.
15. *Wan X., Wang W., Liu J., Tong T.* Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014; 14: 135. DOI: 10.1186/1471-2288-14-135. PMID: 25524443.

16. *Borenstein M.* Introduction to meta-analysis. John Wiley & Sons; 2011: 1-450.*Borenstein M., Hedges L.V., Higgins J.P.T., Rothstein H.R.* Introduction to Meta-Analysis, 2nd Edition. John Wiley & Sons; 2021: 1–544. ISBN: 978-1-119-55835-4.
17. *Sterne J.A.C., Savović J., Page M.J., Elbers R.G., Blencowe N.S., Boutron I., Cates C.J., Cheng H-Y., Corbett M.S., Eldridge S.M., Emberson J.R., Hernán M.A., Hopewell S., Hróbjartsson A., Junqueira D.R., Jüni P., Kirkham J.J., Lasserson T., Li T., McAleenan A., Reeves B.C., Shepperd S., Shrier I., Stewart L.A., Tilling K., White I.R., Whiting P.F., Higgins J.P.T.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019; 366: l4898. DOI: 10.1136/bmj.l4898. PMID: 31462531.
18. *Sterne J.Ac., Hernán M.A., Reeves B.C., Savović J., Berkman N.D., Viswanathan M., Henry D., Altman D.G., Ansari M.T., Boutron I., Carpenter J.R., Chan A-W., Churchill R., Deeks J.J., Hróbjartsson A., Kirkham J., Jüni P., Loke Y.K., Pigott T.D., Ramsay C.R., Regidor D., Rothstein H.R., Sandhu L., Santaguida P.L., Schünemann H.J., Shea B., Shrier I., Tugwell P., Turner L., Valentine J.C., Waddington H., Waters E., Wells G.A., Whiting P.F., Higgins J.P.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016; 355: i4919. DOI: 10.1136/bmj.i4919. PMID: 27733354.
19. *Egger M., Davey Smith G., Schneider M., Minder C.* Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997; 315 (7109): 629–634. DOI: 10.1136/bmj.315.7109.629. PMID: 9310563.
20. *Begg C.B., Mazumdar M.* Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994; 50 (4): 1088–1101. PMID: 7786990
21. *Sterne J.A., Sutton A.J., Ioannidis J.P., Terrin N., Jones D.R., Lau J., Carpenter J., Rücker G., Harbord R.M., Schmid C.H., Tetzlaff J., Deeks J.J., Peters J., Macaskill P., Schwarzer G., Duval S., Altman D.G., Moher D., Higgins J.P.* Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011; 343: d4002. DOI: 10.1136/bmj.d4002. PMID: 21784880.
22. *Kim R., Kawai A., Wakisaka M., Funaoka Y., Ohtani S., Ito M., Kadoya T., Okada M.* Differences in immune response to anesthetics used for day surgery versus hospitalization surgery for breast cancer patients. *Clin Transl Med*. 2017; 6 (1): 34. DOI: 10.1186/s40169-017-0163-4. PMID: 28905322.
23. *Deegan C.A., Murray D., Doran P., Moriarty D.C., Sessler D.I., Mascha E., Kavanagh B.P., Buggy D.J.* Anesthetic technique and the cytokine and matrix metalloproteinase response to primary breast cancer surgery. *Reg Anesth Pain Med*. 2010; 35 (6): 490–495. DOI: 10.1097/AAP.0b013e3181ef4d05. PMID: 20975461.
24. *Cho J.S., Lee M.-H., Kim S.I., Park S.H., Park H.S., Oh E., Lee J.H., Koo B.-N.* The effects of perioperative anesthesia and analgesia on immune function in patients undergoing breast cancer resection: a prospective randomized study. *Int J Med Sci*. 2017; 14 (10): 970–976. DOI: 10.7150/ijms.20064. PMID: 28924368.
25. *Eochagáin A.N., Burns D., Riedel B., Sessler D.I., Buggy D.J.* The effect of anaesthetic technique during primary breast cancer surgery on neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and return to intended oncological therapy. *Anaesthesia*. 2018; 73 (5): 603–611. DOI: 10.1111/anae.14207. PMID: 29457215.
26. *Oh C.-S., Lee J., Yoon T.-G., Seo E.-H., Park H.-J., Piao L., Lee S.-H., Kim S.-H.* Effect of equipotent doses of propofol versus sevoflurane anesthesia on regulatory T cells after breast cancer surgery. *Anesthesiology*. 2018; 129 (5): 921–931. DOI: 10.1097/ALN.0000000000002382. PMID: 30074934.
27. *Lim J.-A., Oh C.-S., Yoon T.-G., Lee J.Y., Lee S.-H., Yoo Y.-B., Yang J.-H., Kim S.-H.* The effect of propofol and sevoflurane on cancer cell, natural killer cell, and cytotoxic T lymphocyte function in patients undergoing breast cancer surgery: an in vitro analysis. *BMC Cancer*. 2018; 18 (1): 159. DOI: 10.1186/s12885-018-4064-8. PMID: 29415668.
28. *Woo J.H., Baik H.J., Kim C.H., Chung R.K., Kim D.Y., Lee G.Y., Chun E.H.* Effect of propofol and desflurane on immune cell populations in breast cancer patients: a randomized trial. *J Korean Med Sci*. 2015; 30 (10): 1503–1508. DOI: 10.3346/jkms.2015.30.10.1503. PMID: 26425050.
29. *Galoș E.V., Tat T.-F., Popa R., Efrimescu C.-I., Finnerty D., Buggy D.J., Ionescu D.C., Mihu C.M.* Neutrophil extracellular trapping and angiogenesis biomarkers after intravenous or inhalation anaesthesia with or without intravenous lidocaine for breast cancer surgery: a prospective, randomised trial. *Br J Anaesth*. 2020; 125 (5): 712–721. DOI: 10.1016/j.bja.2020.05.003. PMID: 32616309.
30. *Enlund M., Berglund A., Andreasson K., Cicek C., Enlund A., Bergkvist L.* The choice of anaesthetic — sevoflurane or propofol — and outcome from cancer surgery: a retrospective analysis. *Ups J Med Sci*. 2014; 119 (3): 251–261. DOI: 10.3109/03009734.2014.922649. PMID: 24857018.
31. *Wigmore T.J., Mohammed K., Jhanji S.* Long-term survival for patients undergoing volatile

versus IV anesthesia for cancer surgery: a retrospective analysis. *Anesthesiology*. 2016; 124 (1): 69–79. DOI: 10.1097/ALN.0000000000000936. PMID: 26556730.

32. *Kim M.H., Kim D.W., Kim J.H., Lee K.Y., Park S., Yoo Y.C.* Does the type of anesthesia really affect the recurrence-free survival after breast cancer surgery? *Oncotarget*. 2017; 8 (52): 90477–90487. DOI: 10.18632/oncotarget.21014. PMID: 29163846.
33. *Yap A., Lopez-Olivo M.A., Dubowitz J., Hiller J., Riedel B; Global Onco-Anesthesia Research Collaboration Group*. Anesthetic technique and cancer outcomes: a meta-analysis of total intravenous versus volatile anesthesia. *Can J Anaesth*. 2019; 66 (5): 546–561. DOI: 10.1007/s12630-019-01330-x. PMID: 30834506.
34. *Pang Q.-Y., Duan L.-P., Jiang Y., Liu H.-L.* Comparison of outcomes after breast cancer surgery between inhalational and propofol-based intravenous anaesthesia: a systematic review and meta-analysis. *J Pain Res*. 2021; 14: 2165–2177. DOI: 10.2147/JPR.S315360. PMID: 34295185.
35. *Leifler K.S., Svensson S., Abrahamsson A., Bendrik C., Robertson J., Gauldie J., Olsson A.-K., Dabrosin C.* Inflammation induced by MMP-9 enhances tumor regression of experimental breast cancer. *J Immunol*. 2013; 190 (8): 4420–4430. DOI: 10.4049/jimmunol.1202610. PMID: 23509357.
36. *Song J., Su H., Zhou Y.-Y., Guo L-.L.* Prognostic value of matrix metalloproteinase 9 expression in breast cancer patients: a meta-analysis. *Asian Pac J Cancer Prev*. 2013; 14 (3): 1615–1621. DOI: 10.7314/apjcp.2013.14.3.1615. PMID: 23679245.
37. *Ren F., Tang R., Zhang X., Madushi W.M., Luo D., Dang Y., Li Z., Wei K., Chen G.* Overexpression of MMP family members functions as prognostic biomarker for breast cancer patients: a systematic review and meta-analysis. *PLoS One*. 2015; 10 (8): e0135544. DOI: 10.1371/journal.pone.0135544. PMID: 26270045.
38. *Baiardo Redaelli M., Belletti A., Monti G., Lembo R., Ortalda A., Landoni G., Bellomo R.* The impact of non-blinding in critical care medicine trials. *J Crit Care*. 2018; 48: 414–417. DOI: 10.1016/j.jcrc.2018.09.031. PMID: 30317050.
39. *Baiardo Redaelli M., Landoni G., Di Sanzo S., Frassoni S., Sartini C., Cabrini L., Monti G., Scandroglio M., Zangrillo A., Bellomo R.* Interventions affecting mortality in critically ill and perioperative patients: a systematic review of contemporary trials. *J Crit Care*. 2017; 41: 107–111. DOI: 10.1016/j.jcrc.2017.05.005. PMID: 28505485.

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