REVIEW ARTICLE
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The impact of anesthetic techniques on breast cancer recurrence: a systematic review of clinical evidence

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ABSTRACT

Introduction: Surgery is the most effective treatment for breast cancer; however, several factors can impair the immune system during the perioperative period, including the anesthetic technique. Since metastasis is the leading cause of death, one of the treatment pillars is to prevent cancer progression. This systematic review will focus on the prospective clinical evidence available on anesthesia's role in favoring breast cancer recurrence. **Methods:** The Cochrane Library, Medline, Embase, LILACs, and Web of Science were electronically searched from inception through December 2020 for randomized controlled trials assessing the association of postoperative recurrence and survival with the use of regional anesthesia, opioids, anesthetic adjuncts, and general anesthesia during surgical resection of breast cancer. In total, 711 articles were retrieved. After title and abstract screening and full-text reviews, five randomized controlled trials were selected. **Results:** Two studies compared inhalation anesthesia with total intravenous anesthesia, while three compared general anesthesia with regional anesthesia and analgesia. There was no significant association between the anesthetic technique and local recurrence, metastasis, or survival. **Conclusion:** This systematic review did not find an association between the type of anesthesia performed and a higher breast cancer recurrence rate. Up to this time, there is no clinical evidence to support a specific anesthetic technique for malignant breast tumor resection surgeries.

KEYWORDS: breast neoplasms; recurrence; anesthesia.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women globally, with 1.7 million diagnoses every year[1] and second in line for the most common cause of cancer-related death[2]. Surgery resection treats a large number of malignant tumors; breast cancer is no exception. Early detection of localized or regional breast cancer can procure a 99%4-85% 5-year survival rate[3], with 97% of women in stages I or II experiencing surgery[4]. Therefore, perioperative management may interfere with oncological outcomes.

Several risk factors impair the immune system during the perioperative period[5]. Pain, blood transfusion, hypothermia, and anesthetic technique cause immunosuppression, allowing cancerous cells to migrate to distant organs[6] — even surgical manipulation can release micrometastasis into the circulation, along with the acute inflammatory response that extensive surgery entails[7].

Metastasis is the major cause of death in breast cancer patients, with a 30% incidence rate[8]: therefore, preventing recurrence is of paramount importance. A new era of research has emerged in the anesthesia field. Each anesthetic technique affects cancer cells in a particular way. Regional anesthesia reduces surgical stress, inflammatory response, and opioid consumption[9-11]. Local anesthetics (LAs) have shown antiproliferative and cytotoxic effects against *in vitro*[12] tumor cells. Sevoflurane suppresses the immune system by decreasing Natural Killer (NK) cells' activity, promoting T-lymphocyte apoptosis and increasing pro-inflammatory cytokines[13-15]. Opioids have a more complex role on cancer recurrence[16]: a low dose can elicit tumor growth via angiogenesis and down-regulation of the immune response, while high concentrations may curb tumor growth. The opioid receptors κ and μ act divergently, with the former promoting and the latter inducing a pro-inflammatory response[17].

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A myriad of retrospective studies suggests that volatile anesthetics and opioid anesthesia promote breast cancer recurrence compared to propofol-based and regional anesthesia[18-20]. Exadaktylos et al.[18] reported that women had a significantly lower risk of cancer recurrence if submitted to a combination of propofol and thoracic paravertebral block (TPVB) compared to balanced general anesthesia (GA) with sevoflurane and opioids. However, the anesthetic technique of choice for mastectomies is still debatable.

This systematic review focused on the clinical evidence available on the role of anesthesia regarding breast cancer recurrence. To the extent of our knowledge, it was the first to compare only prospective randomized control trials. We described the data and critically analyzed randomized clinical trials on the use of regional anesthesia, opioids, anesthetics adjuncts, and GA in patients undergoing breast cancer resection.

METHODS

This systematic review was conducted according to the Cochrane Handbook for Systematic Reviews and Interventions[21] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[22]. The study protocol was published on Open Science Framework,

Search strategy

We conducted an electronic search of the following databases (from inception through December 2, 2020): Cochrane Library and Cochrane Trials Register, Medline, Embase, LILACs, and Web of Science; no language limitation was enforced. Search terms included: "Breast Cancer", "Anesthetic Technique" or "Regional Anesthesia" or "General Anesthesia", "Propofol" or "Sevoflurane", "Disease Free Survival" or "Recurrence" or "Metastasis". The complete list of search terms is attached in the online Appendix 1. Manually, we performed a thorough search within oncological and anesthesia society websites, annals of congresses, and articles' reference lists. Ongoing clinical trials were also assembled by searching the combination "breast neoplasms" at https://clinicaltrials.gov/[23].

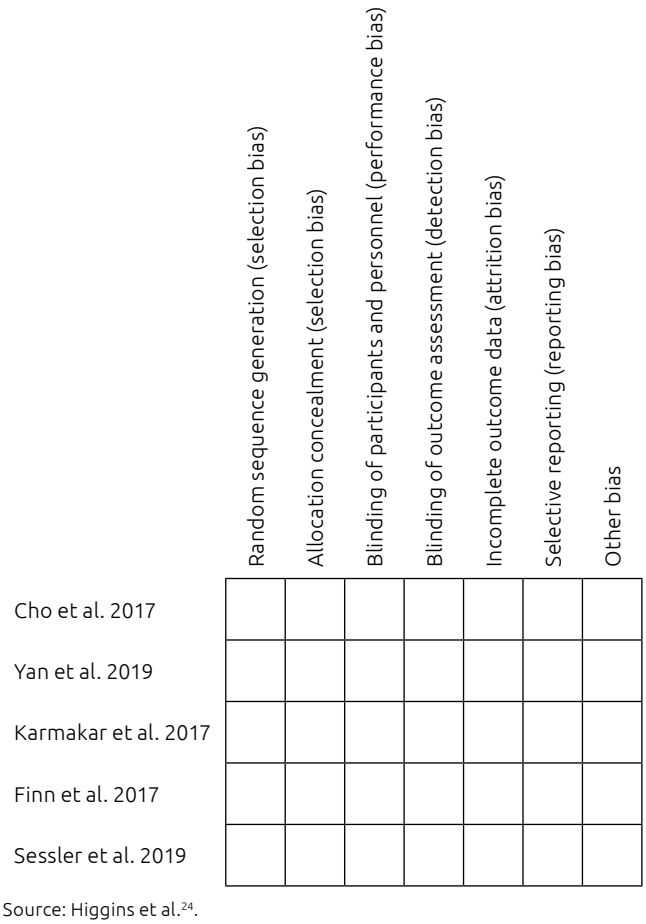
Study selection and data extraction

The inclusion criteria were threefold: randomized controlled clinical trials (RCT), surgery for resection of malignant breast tumor in female over 18 years old, and three possible interventions' scenarios — comparing the use of regional anesthesia, either isolated or combined to general anesthesia, with general anesthesia; comparing volatile anesthesia with total intravenous anesthesia; comparing opioid-free anesthesia with opioids. Studies depicting metastatic disease were excluded. The primary outcome was postoperative cancer recurrence, defined as locoregional recurrence and distant metastasis. The secondary outcomes were overall survival and recurrence-free survival.

Two of the authors (A.D., D.S.) independently assessed titles and abstracts for admittance into this review. If any divergence of judgment were manifested, a third author (A.A.) would settle. The data were extracted in a standardized way through an electronic form. Apart from measured outcomes and types of interventions, other extracted data included study-related information, such as author, year of publication, sample, follow-up time, and conclusions. Given methodological diversity and statistical heterogeneity, a meta-analysis was not conducted. Instead, a systematic review of the applicable clinical evidence was completed.

Risk of bias

We covered six domains for assessing the risk of individual bias[24]: selection bias, performance bias, detection bias, attrition bias, reporting bias, and others. A high risk of bias is considered when the studies fall out of these criteria. Two authors independently appraised these risks for the breast cancer recurrence outcome, which are summarized in Figure 1.



Source: Higgins et al.[24].

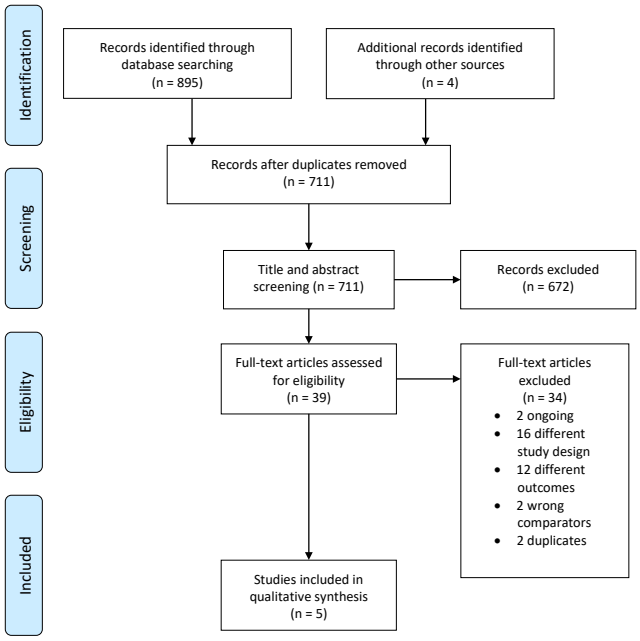
Figure 1. Risk of bias summary.

RESULTS

The electronic and manual search found 899 studies, 711 of them eligible for title and abstract review. Six hundred and seventy-two studies were deemed irrelevant, while 39 were singled out for full-text reading and quality assessment. Lastly, five clinical trials were selected for data extraction (Figure 2).

Two studies compared the association of inhalation anesthesia and total intravenous anesthesia (TIVA) (Table 1) on cancer recurrence rates, metastasis, recurrence-free survival (RFS), and overall survival (OS). Both included patients with breast cancer stage 0-III, and the type of surgery performed varied from breast-conserving surgery to radical mastectomy, with no significant difference between the groups. Cho et al.[25] followed 48 women for two years to find that only one patient in the sevoflurane-fentanyl (SEVO) group had a recurrence in the contralateral breast without statistical significance. Yan et al.[26] also investigated short-term cancer recurrence in 80 women for the same amount of time. The two-year RFS rate in the SEVO and TIVA groups for the first and second studies, respectively, averaged 89.5% and 97.6% (p = 0.138) while the two-year OS rate did 92.8% and 100% (p = 0.182).

The other three studies investigated cancer recurrence by comparing general anesthesia with regional anesthesia and analgesia (Table 2). Finn et al.[27] followed 54 women for five years — all underwent mastectomy with balanced GA and thoracic paravertebral block (TPVB), but, for 72 hours after surgery, one group received a perineural infusion of ropivacaine while the other received saline (placebo). No significant association between the anesthesia technique and cancer recurrence was observed. Karmakar et al.[28] followed 173 women for five years after a modified radical mastectomy and used a similar method of a continuous TPVB. The women were randomized into three groups: control, perineural infusion with saline (placebo), and perineural infusion with ropivacaine; all of them received total intravenous GA with propofol. Each group incidences of local cancer recurrence, metastasis, and all-cause mortality were 2.3% (95%CI 0.7–5.4%), 7.9% (95%CI 4.6–12.6%), and 6.8% (95%CI 3.6–11.2%), respectively. These studies did not discriminate in which breast cancer stage the patients were admitted.



Source: Shamseer et al.[22].

Figure 2. PRISMA flow diagram.

Table 1. Summary of trials comparing total intravenous general anesthesia versus balanced general anesthesia.

Author	Year	Study design	Tumor stage	Type of surgery	Intervention	Groups		Outcome	Follow-up time	Conclusion	Observations
						TIVA (n = 24)	*SEVO (n = 24)*				
Cho et al.[25]	2017	RCT	0-III	Partial mastectomy, total mastectomy, radical mastectomy	TIVA vs GA with volatile anesthetic	Propofol (TCI) + Ketorolac (60 mg)	Sevoflurane (according to BIS) + Fentanyl (50 mcg)	Incidence of cancer recurrence and metastasis	2 years	No significant association between anesthesia technique and recurrence was observed.	Both groups used remifentanil and tramadol.
						TIVA (n = 42)	*SEVO (n = 38)*				
Yan et al.[26]	2019	RCT	0-III	BCS, mastectomy with or without axillary lymph node dissection	TIVA vs GA with volatile anesthetic	Propofol 3-6 mg/kg/h	Sevoflurane 1.5-2% (according to BIS)	Incidence of cancer recurrence, RFS and OS	2 years	No significant association between anesthesia technique and recurrence was observed.	Both groups used fentanyl and flurbiprofen.

RCT: randomized controlled trial; TCI: target control infusion; TIVA: total intravenous anesthesia; SEVO: Sevoflurane; BIS: Bispectral index; RFS: recurrence free survival; OS: overall survival; BCS: breast conserving sugery.

Table 2. Summary of trials comparing general anesthesia versus regional anesthesia.

Author	Year	Study design	Tumor stage	Type of surgery	Intervention	Groups			Outcome	Follow-up time	Conclusion	Observations
Finn et al.[27]	2017	RCT	N/A	Unilateral or bilateral mastectomy with or without axillary lymph node dissection	General anesthesia + single dose RA vs GA + continuous dose RA	Control (n = 28)		LA (n = 26)	Incidence of cancer recurrence and OS	5 years	No significant association between anesthesia technique and recurrence was observed.	All patients received nitrous oxide, acetaminophen and intravenous opioid (fentanyl or hydromorphone or morphine)
						GA (sevoflurane) + TPVBs (ropivacaine 0,5% 15 ml + saline 72h)		GA (sevoflurane) + TPVBc (ropivacaine 0,5% 15 ml + ropivacaine 0,4% 72h)				
Karmakar et al.[28]	2017	RCT	N/A	Radical mastectomy	General anesthesia vs GA + single dose RA vs GA + continuous dose RA	*Control (n = 58)*	*Saline (n = 56)*	*LA (n = 59)*	Incidence of cancer recurrence, metastasis and OS	5 years	No significant association between anesthesia technique and recurrence was observed.	All patients received a propofol-based anesthesia
						TIVA (propofol)	TIVA (propofol) + TPVBs (ropivacaine 2 mg/kg + saline 72h)	TIVA (propofol) + TPVBc (ropivacaine 2 mg/kg + ropivacaine 0.25% 72 h)				
Sessler et al.[29]	2019	RCT	0-III	Simple mastectomy, modified mastectomy, wide local excision with node dissection	General anesthesia vs regional anesthesia	Control (n = 1,065)		LA (n = 1,043)	Incidence of cancer recurrence	36 months	No significant association between anesthesia technique and recurrence was observed.	Both groups used propofol, fentanyl and morphine
						GA (sevoflurane)		TPVB (bupivacaine 0.5% or ropivacaine 0.5% 10-20mL) + ropivacaine 0.1–0.2% 48 h)				

RCT: randomized controlled trial; GA: general anesthesia; RA: regional anesthesia; TIVA: total intravenous anesthesia; LA: local anesthetic; TPVB: thoracic paravertebral block (s: single; c: continuous); TEB: thoracic epidural block; OS, overall survival; N/A: not available.

The third study is a multicenter, prospective, randomized trial conducted by Sessler et al.[29]. Over two thousand women, initially classified as breast cancer stage 0-III, were accompanied for a median follow-up of 36 (IQR 24–49) months and divided into two groups: regional anesthesia-analgesia (n = 1,043) and general anesthesia and opioid analgesia (n = 1,065). The first group received a thoracic epidural or a paravertebral block with a continuous catheter infusion of local anesthetic for postoperative analgesia. In the second group, anesthesia was maintained with sevoflurane, and the patients received morphine sulfate at the end of the surgery. The groups reported 102 (10%) against 111 (10%) recurrences, respectively (HR = 0.97, 95%CI 0.74–1.28; P = 0.84), indicating that regional anesthesia did not reduce breast cancer recurrence.

A meta-analysis was not conducted due to the diverseness in general anesthesia techniques, local anesthetics used for TPVB, and tumor staging permeating each study.

DISCUSSION

Our research showed no significant statistical association between anesthetic technique and higher breast cancer recurrence rate. Since our review was limited to randomized clinical trials, only five studies could be considered, although a few ongoing clinical trials may publish results in the following years (Table 3).

We divided our findings into two groups: intravenous anesthesia versus volatile anesthesia and general anesthesia (GA) versus GA combined with regional techniques (Table 1). In the first group, neither study reported intervention-related benefits.

Table 3. Summary of ongoing clinical trials registered on Clinicaltrials.gov.

Trial number	Study Title	Interventions
NCT03109990	Impact of Dexmedetomidine on Breast Cancer Recurrence After Surgery	•Drug: Dexmedetomidine •Drug: Saline
NCT03941223	Regional Anesthesia for Breast Surgery	•Procedure: PECSII and paravertebral blocks
NCT01204242	IV Lidocaine for Patients Undergoing Primary Breast Cancer Surgery: Effects on Postoperative Recovery and Cancer Recurrence	•Drug: Lidocaine •Drug: Saline
NCT03117894	PECS-2 for Breast Surgery	•Procedure: PECS-2

PECS2: pectoral nerve block type 2.

This finding contradicts Wigmore et al.[30], who, in a 2016 retrospective study with over 7,000 cancer patients, reported an approximately 50% higher mortality rate for volatile anesthesia against intravenous anesthesia, with an adjusted hazard ratio of 1.46 (1.29 to 1.66).

Cho et al.[25] compared two groups with different anesthetic techniques and analgesia: a propofol-ketorolac group (TIVA) and a sevoflurane-fentanyl group (SEVO), investigating the effect of these techniques in the cytotoxicity of natural killer cells and tumor recurrence up to two years after surgery. Cancer metastasis did not occur in either group, in spite of different drug properties. Propofol has cyclooxygenase (COX-2) inhibiting activity, which reduces the production of prostaglandin E2 (PGE2), a mediator of pain and inflammation[31]. Ketorolac also impedes prostaglandin synthesis via the inhibition of the COX enzyme, above its antitumor and anti-angiogenic properties[32]. Volatile anesthetics and fentanyl, though, suppress NK cells and T lymphocytes[33,34].

Pain causes immunosuppression[35]; however, since both groups had a similar analgesic efficacy, the authors could eliminate it as a contributing factor. Pain scores were assessed using an 11-point numerical rating scale (NRS) at 30 minutes, 6 hours, 24h, and 48h postoperatively. If the patients complained of an NRS ≥ 4 pain, ketorolac and propacetamol were given to the TIVA group and fentanyl to the SEVO group. Since both groups received different analgesic drugs, the authors could not discriminate each drug's effects on inflammatory response. Another limitation of the study was that all patients received remifentanil intraoperatively and tramadol for postoperative pain control — even though they are not considered immunosuppressive drugs and the doses were equivalent between the groups[36,37], we cannot exclude their opioid effect.

Yan et al.[26] had a short-term recurrence rate of breast cancer in five (6.3%) patients, four SEVO and one TIVA, during 28 months of follow-up. Two deaths were observed, both in the volatile group. No difference was found between RFS (p = 0.953) and OS (p = 0.281) between the two anesthetic techniques. Propofol was used for anesthetic induction in both groups, and fentanyl and flurbiprofen were given to all patients to provide postoperative analgesia. Those interventions could make it difficult to differentiate the individual properties of sevoflurane and propofol in the immune response. However, the study aimed to compare different anesthetic techniques rather than just different drugs.

In both Cho's and Yan's studies, we found puzzling elements and could not observe benefits from either anesthetic technique. Besides, the short-term RFS of breast cancer was elevated[38], which would require a large sample and a longer follow-up to detect any significant difference.

Forget et al.[39] had already suggested that non-steroidal anti-inflammatory drugs (NSAIDs) given shortly before surgery produce antitumor effects. Fentanyl has also demonstrated antitumor properties by inhibiting cancer cell migration and invasion[40];

however, in a large Danish cohort population study, opioid use showed no clinically significant association with breast cancer recurrence[41]. Thus, the effects of opioids on tumor growth and metastasis are complex and controversial: they may play a beneficial role, but it depends on drug concentration, duration of exposure, and even cancer type[16,42].

In 2006, the first study to describe a positive relationship between regional anesthesia and breast tumor propagation, by Exadaktylos et al.[18], showed the recurrence rate for the sevoflurane-fentanyl group as four times higher than the propofol-paravertebral block group. On the other hand, Kairaluoma et al.[43], in 2016, published a similar retrospective study following 86 women for 12 years; the results did not demonstrate any anti-metastatic effect of perioperative regional anesthesia.

Our second group of studies, which analyzed regional techniques, culminated in findings analogous to Kairaluoma et al's. Karmakar et al.[28] compared TIVA with GA combined with TPVB and a third group that used postoperative transcatheter analgesia. There was no difference in the risk of local cancer recurrence, metastasis, or all-cause mortality between the groups ($p = 0.79$, $p = 0.91$, and $p = 0.13$, respectively). When compared to the group which received only GA, the risk of local recurrence or metastasis agreed with that for patients in the GA plus single-TPVB group (HR = 1.11, 95%CI 0.32–3.83) or the GA plus continuous-TPVB group (HR = 0.79, 95%CI 0.21–2.96).

Since all patients received total intravenous anesthesia with propofol, it is questioned whether this could camouflage the regional anesthesia technique's anti-inflammatory perk. As explained earlier, propofol has numerous documented positive effects on the immune system function[14,31,44], so that the TIVA components may have conferred this immunoprotective benefit. In contrast, using a single general anesthesia technique helped to evaluate how regional anesthesia affected the recurrence rate.

Finn et al.[27] concluded that adding a continuous ropivacaine infusion to a single-injection paravertebral block in the immediate postoperative period did not decrease the post-mastectomy cancer recurrence risk. Five out of 54 (9.3%) patients suffered from recurrence: three among those in the ropivacaine group (11.5%) and two in the saline group (7.1%; $p = 0.92$). Nevertheless, we should also consider that single-injection ropivacaine was administered to all patients, which might have decreased surgical stress in both treatment groups — ropivacaine can provide 8-16 hours of analgesia. Therefore, albeit not always an obvious choice, regional anesthesia is a technique with proven benefits; with the TPVB comes less chronic pain and better postoperative physical and mental performance[45].

Sessler et al.[29] was a much-expected multicenter trial. A large sample and well-designed study, it proved the irrelevance of the regional anesthetic technique in attaining less tumoral occurrence. Nonetheless, there is space for reservations, as has already been discussed[46-49]. Firstly, anesthetic techniques overlapped, with the concurrent use of fentanyl, propofol, and morphine in all patients and the supplementation of sevoflurane in 17% of the patients from the paravertebral block group. This combined use of opioids and volatile anesthetic with the regional technique might have interfered with its benefit. Secondly, the average follow-up of 36 months can be considered a short time to assess tumor recurrence. Finally, better screening and superior protocol regimens have decreased breast cancer mortality rates over the last decade[50], meaning the clinical treatment of the disease itself has evolved[51] during the total general study period of 12 years.

The temporary immune changes caused by anesthetic drugs do not seem to bring long-term repercussions. Despite the paucity of relevant randomized controlled trials, where just one avails a high level of evidence, our qualitative analyses did not find an association between the type of anesthesia performed and the prognosis in breast cancer patients. Neither regional nor total intravenous anesthetic techniques showed significantly superior outcomes when compared to general anesthesia.

Our research's primary limitations were the narrow set of applicable studies, the significant heterogeneity, the small sample size and short follow-up time from some trials, and the high or unclear risk of bias from most included studies. This type of review suffers from difficulty to standardize in order to reduce bias. It is impossible to blind the anesthesiologist who will administer distinct techniques. Besides, each trial adopted different doses and concentrations, and the disease itself bears multiple stages. The stage and grade of the tumors and the surgical management variables presented a good distribution among the study groups, but most women were diagnosed in the early stages, which naturally translates to fewer recurrence rates[3]. Due to this low incidence of recurrence, the validation of the findings might prove difficult, even with significant statistical differences. There are yet other questions that may raise bias for this type of controlled trial: does breast cancer surgery stress is enough to cause immunosuppression? Does the natural evolution of anti-cancer therapies inhibit the *in-vitro*-proved[52,53] harmful effects of anesthetics? Therefore, we suggest choosing the best available technique, considering patient comorbidities and particularities.

CONCLUSION

This review did not find an association between the type of anesthesia performed and the long-term prognosis in patients with breast cancer. It points out to no clinical evidence currently supporting a specific anesthetic technique for malignant breast tumor resection surgeries. However, the scarcity of high-quality randomized clinical trials on the subject, with larger samples and longer follow-up times demands further research.

AUTHORS' CONTRIBUTION

A.D.: conceptualization, investigation, methodology, data acquisition, formal analysis, writing – first draft, writing – review & editing; A.A.: conceptualization, investigation, methodology, data acquisition, formal analysis, writing – first draft; D.S.: conceptualization, investigation, methodology, data acquisition, formal analysis, writing – review & editing; J.L.A.: conceptualization, methodology, formal analysis, writing – review & editing.

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