Occurrence and Risk Factors with Axillary Network Syndrome after Breast Cancer Treatment: Systematic Review with Meta-analysis

doi: https://doi.org/10.32635/2176-9745.RBC.2023v69n3.3877

Síndrome da Rede Axilar após Tratamento para Câncer de Mama: Revisão Sistemática com Metanálise

Ocurrencia y Factores Asociados con el Síndrome de la Red Axilar después del Tratamiento del Cáncer de Mama: Revisión Sistemática con Metaanálisis

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ABSTRACT

Introduction: Breast cancer is the most common in women and surgery is the main treatment of choice. Axillary Web Syndrome (AWS) is a recurrent condition that occurs in up to 86% after surgery, presenting as a single cord or multiple cords in the subcutaneous tissues of the ipsilateral axilla, causing pain and limitation of movement. **Objective:** To investigate studies about the occurrence and factors associated with AWS post breast cancer treatment**. Method:** Systematic review with meta-analysis based in the PECOS methodology according to PRISMA guidelines at the databases PubMed, LILACS and EMBASE. **Results:** Five articles were selected with rate of occurrence of 35% of AWS. The associated factors found showed a minor relative risk (RR) of recurrence in those who underwent sentinel lymph node biopsy compared to those who were submitted to axillary dissection (RR 0.49; 95%CI [0.42;0.57] I^2=95%, p=0.01). The appearance of AWS ranged from 35% to 39% in patients who submitted to chemotherapy and radiotherapy, but the type of surgery did not have a statistically significant result for triggering the syndrome. **Conclusion:** Individuals who underwent sentinel lymph node biopsy are less likely to develop the syndrome when compared to those who submitted to axillary dissection. Oncological therapies had similar percentages for the appearance of AWS and the type of surgery did not interfere in the evolution of the pathology.

Key words: breast neoplasms; lymphatic diseases; risk factors; axilla.

RESUMO

Introdução: O câncer de mama é o mais incidente nas mulheres e a cirurgia é o principal tratamento de escolha. A síndrome da rede axilar (SRA) é uma condição recorrente que ocorre em até 86% das pacientes após cirurgia, se apresenta como um único cordão ou múltiplos cordões nos tecidos subcutâneos da axila ipsilateral e gera dor e limitação do movimento. **Objetivo:** Investigar estudos sobre a ocorrência e fatores associados à SRA após tratamento do câncer de mama. **Método:** Revisão sistemática com metanálise, nas bases de dados PubMed, LILACS e EMBASE, com a metodologia PECOS, seguindo a diretriz PRISMA. **Resultados:** Cinco artigos foram selecionados, com taxa de ocorrência da SRA de 35%. Os fatores associados encontrados apresentaram um menor risco relativo (RR) de recorrência para quem realizou biópsia de linfonodo sentinela em comparação aos que se submeteram à dissecção axilar (RR 0,49; IC 95% [0,42; 0,57] I^2=95%, *p*=0,01). Houve uma variação de 35% a 39% de desenvolvimento para a SRA em pacientes que se submeteram à quimioterapia e radioterapia, porém o tipo de cirurgia não teve resultado estatisticamente significativo para o desencadeamento da síndrome. **Conclusão:** Indivíduos que realizaram biópsia de linfonodo sentinela têm menos chance de desenvolver a SRA quando comparados aos que fizeram dissecção axilar. As terapias oncológicas apresentaram proporções parecidas de aparecimento da SRA e o tipo de cirurgia não interferiu na evolução da patologia.

Palavras-chave: neoplasias da mama; doenças linfáticas; fatores de risco; axila.

RESUMEN

Introducción: El cáncer de mama es el más común en las mujeres e la cirugía es considerada el tratamiento de elección. El síndrome de la red axilar (SRA) es una condición recurrente que ocurre hasta en un 86% de las pacientes después de la cirugía, se presenta como un cordón único o múltiples cordones en los tejidos subcutáneos de la axila isolateral, y causa dolor y limitación del movimiento. **Objetivo:** Investigar estudios sobre la ocurrencia y factores asociados al SRA después del tratamiento del cáncer de mama. **Método:** Revisión sistemática con metaanálisis, en las bases de datos PubMed, LILACS y EMBASE, con la metodología PECOS, siguiendo la guía PRISMA. **Resultados:** Se seleccionaron cinco artículos, con la tasa de ocurrencia del SRA del 35%. Los factores asociados encontrados mostraron un menor riesgo relativo (RR) de recurrencia para quien realizó biopsia de ganglio centinela en comparación con las que se sometieron a la disección axilar (RR 0,49; IC 95% [0,42;0,57] I^2=95%, p=0,01). Hubo una variación del 35% al 39% de desarrollo del SRA en pacientes que se sometieron a la quimioterapia y radioterapia, aunque el tipo de cirugía no tuvo un resultado estadísticamente significativo para desencadenar el síndrome. **Conclusión:** Las personas que se sometieron a una biopsia de ganglio centinela tienen menos probabilidades de desarrollar el SRA en comparación con aquellas que se sometieron a disección axilar. Las terapias oncológicas presentaron proporciones parecidas de aparición del SRA y el tipo de cirugía no interfirió en la evolución de la patología.

Palabras clave: neoplasias de la mama; enfermedades linfáticas; factores de riesgo; axila.

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INTRODUCTION

Breast cancer is the most frequent type in women and is considered a major public health problem, with 1,384,155 new cases estimated worldwide and 459,000 related deaths[1]. The worldwide incidence of female breast cancer is predicted to reach approximately 3.2 million new cases per year by 2050. These numbers reflect the magnitude of the incidence of this type of cancer, its effect on world society and the need for urgent preventive and treatment measures[1].

Risk factors for the development of breast cancer vary in modifiable and non-modifiable factors [2]. The female gender is often the most affected, happening rarely in the male population in about only 1% of cases. Age is also considered an important risk factor, the incidence rate increases significantly at menopause and then gradually decreases or remains constant[2,3]. Hereditary factors are also fully related, such as family history of cancer, high breast density etc.[2,4]. Modern lifestyles such as excessive alcohol consumption, dietary fat intake, exposure to tobacco and ionizing radiation may increase the risk of development[4,5].

Surgery is the treatment of choice and can be mastectomy or conservative surgery[1,3]. Mastectomy can be classified in three simple ways: the most common type, in which there is the removal of the entire breast including the nipples, but there is no removal of axillary lymph nodes; modified radical: elliptical incision, including the nipple-areolar complex, removal of all breast tissue, as well as the pectoralis major, and also the removal of axillary lymph nodes[3,4]; and sparing skin and nipples: most of the skin is preserved, it is done in women who have a smaller tumor and at an early stage.

Conservative surgery can be described by several terms, including quadrantectomy, lumpectomy or partial mastectomy – which consists of removing the segment or sector of the breast where the tumor process is located[3,4]. Often, these include sentinel lymph node biopsy (SLB): removal of compromised lymph nodes only – which generates less damage to the axillary chain, a key component also in the staging of patients with early-stage breast cancer who have clinically negative lymph nodes; or lymphadenectomy/dissection of axillary lymph nodes: removal of lymph nodes located in the tumor region; in these cases, there is greater involvement of the axillary chain [1,2]. In addition, chemotherapy and radiotherapy are used as adjuvants in cancer treatment [1,2]. These procedures are important to predict prognosis, reduce recurrence and promote adequate treatment[1,2]. However, the axillary surgical approach leads to significant short- and long-term complications such as pain, paresthesia, lymphedema, axillary network syndrome (Ras), and decreased range of motion (ROM)[1,2].

Ras is a common condition that occurs in up to 86% of patients after surgery, with axillary lymph node dissection[3-5]. It presents as a single strand or multiple thin strands in the subcutaneous tissues of the ipsilateral axilla[3-5]. Some authors claim that the condition occurs through a rupture in the lymphatic system during lymph node resection, with interruption of the flow, which causes thrombosis and inflammation, generates transformation in the veins and lymphatic vessels, and thus the formation of fibrotic bands [3-5]. It often becomes symptomatic between two and eight weeks postoperatively but can also develop months to years after surgery[3-5]. These cords are located in an area from the armpit to the medial surface of the upper part and the forearm, and can be visible and palpable, this generates a limitation of the ROM of the shoulder ipsilateral to the surgical process and the presence of axillary pain that extends from the elbow to the wrist[3-5].

Only a few studies have investigated the occurrence and the main factors associated with the development of SARS. Of these, axillary lymph node dissection, type of breast surgery performed, chemotherapy, radiotherapy, among others, are currently considered factors for its development[6-8]. Due to the observed increase in women with this condition, secondary to breast cancer, presenting limitations that directly interfere with quality of life, and also the lack of accurate studies based on the scientific literature, it is necessary to know the causes and associated factors, being of important relevance for clinical practice and adequate management. Thus, the objective of this article is to investigate in the scientific databases studies on the occurrence and factors associated with SARS after treatment for breast cancer.

METHOD

Systematic review with meta-analysis whose elaboration followed the recommendations proposed by the Cochrane Collaboration [9] and the Preferred Reporting Items for Systematical Review and Meta-Analyses: The PRISMA Statement[10,11] through the acronym PECOS (P=participants, E=exposure, C=comparison, O=outcome, S=design of eligible studies)[11], which involves analysis, evaluation, and integration of the relevant literature. This study is registered in the systematic reviews database of the International Prospective Register of Systematic Reviews (PROSPERO) with ID CRD42022349538.

To achieve all the relevant evidence, observational studies (cross-sectional, cohort and case-control) were searched without restriction as to the period of publication and language, which included in the sample only people

with breast cancer, regardless of age, female sex, type of surgical procedure, associated with the performance of axillary procedure (lymphadenectomy/axillary dissection or BLS), which presented Ras and related factors.

Studies from non-primary sources were excluded, such as literature reviews, studies that did not meet the guiding question of the research, duplicates in more than one database, animal research, *in vitro* studies, studies that addressed other types of cancer, and studies in which the population was not fully composed of people with SARS associated with breast cancer.

Observational studies were included, according to the PRISMA[10] methodology, through the selection process using the international guidelines of the Cochrane Handbook for Systematic Reviews of Interventions[9]. In addition, the acronym PECOS[11] was applied. Participants: patients with breast cancer; exposure: occurrence and factors associated with Ras (type of surgery, axillary procedure performed etc.); comparison: patients who did not present the outcome of SARS; outcome: presentation of SARS; and design of eligible studies: observational studies.

The search steps occurred using the following electronic databases PubMed, EMBASE and LILACS.

The terms used are indexed in the Descriptors in Health Sciences (DeCS) and Medical Subject Headings (MeSH), and their correspondents in English and Portuguese connected through *Boolean* operators "AND" and "OR". The research descriptors included: breast neoplasms (*lobular carcinoma in situ; breast neoplasms; breast cancer*), lymphatic diseases (*axillary dissection*; *axillary lymph node dissection; lymphatic diseases*) and risk factors (*risk factors; risk assessment; risk adjustment*).

The search was carried out through the *Rayyan* application with the inclusion of all articles found from the elaborated search strategy, analyzed by two reviewers independently and later compared. Initially, the articles were selected by reading the title and abstract; and then the full reading was performed, remaining those that met the aforementioned eligibility criteria.

The information was collected by a reviewer, using a standardized form with data related to the study and the sample: type of study, sample size, profile of participants, associated comorbidities, history of diseases, clinical staging of the pathology; and details of the intervention: type of surgery, axillary procedure, cancer therapy, presence of SARS, occurrence and associated factors, duration of the study and results obtained, checked by a second reviewer, with the objective of categorizing and organizing the data found. Any divergence was discussed until a consensus was reached, with the participation of a third evaluator, if necessary.

The studies were evaluated for the risk of bias using The Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I)[12]. The process is based on domains and structured through guiding questions for the judgment of each domain, also directed to the evaluation of outcomes individually, by two researchers independently. It covers seven domains, separated into three subcategories. Before the intervention: bias by confounding; and bias in the selection of participants. In the intervention: bias in the classification of interventions. After the intervention: bias due to deviation from the intended interventions; bias due to missing data; bias in the measure of outcomes; and bias in the selection of results.

The first two assess issues that need to be compared in the groups under study at baseline, before the implementation of the intervention, and are composed of confusion bias and selection of participants. The third classifies the intervention itself. The following four assess the risk of bias that may be present after the implementation of the intervention: deviation from the intended intervention, loss of data, measurement of the outcome and selective reporting of the results obtained. The judgment options of each domain are: low risk of bias, moderate risk of bias, severe risk of bias, critical risk of bias or no information. Judgments within each domain lead to an overall risk of bias judgment for the outcome being evaluated.

The meta-analysis was performed *using RStudio* version 4.2.1, using the common effects model, and the effect measures were obtained by the post-event values of the main variables found in common in the elected studies. An alpha value of 0.05 and a 95% confidence interval (95% CI) were considered statistically significant. The statistical heterogeneity of treatment effects between studies was assessed by the inconsistency index (I^2), in which values >25% were considered to indicate substantial heterogeneity.

The studies were evaluated for the level of evidence by two evaluators independently, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool[13], a universal and sensitive system to judge the general certainty of each outcome. The classification happens in four levels: high, moderate, low and very low. Two independent researchers evaluated the study design, risk of overall bias, inconsistency, indirect evidence, inaccuracy, and publication bias according to the guidelines. Any disagreements between the evaluators were resolved in a consensus meeting.

RESULTS

The path followed for the selection of studies began with the search in the databases with the descriptors

already mentioned, and 10,213 references were identified from the searches. Of these studies, five were considered of potential relevance with complete data extraction, and meta-analysis can be performed, according to the flowchart (Figure 1).

To calculate the risk of bias, that is, to evaluate the methodological quality of the studies, the ROBINS-I was used. Three studies presented low risk and two moderate risk. Thus, the final result had 80% of low risk of bias and 20% of some concerns with bias, especially those who presented moderate risk due to the exclusion of the participants due to lack of data on other variables necessary for the analysis, directly interfering in the measurement of the results obtained and in the follow-up time, being the main factors found. Finally, the evaluation was weighted according to the ROBINS-I protocol.

Having evaluated all domains, an overall risk of bias was established for each study (Chart 1).

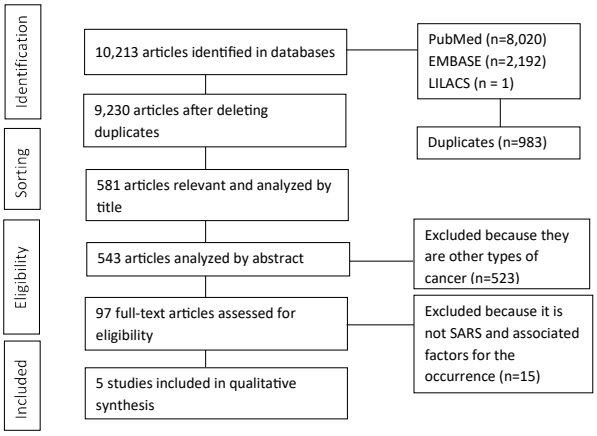


Figure 1. Flowchart of the study selection process and screening results

Thus, the studies were organized in tables and specified as to the authors, year, characteristics of the participants, type of surgery performed, oncological treatment, presence of SARS, intervention, time for its occurrence, as well as resolution, main associated factors and results obtained (Table 1)[14-18]. All studies included in this review are retrospective, cohort or case-control.

The results were synthesized and presented containing the occurrence and the main common factors associated with Ras, such as the proportion of occurrence, chemotherapy, radiotherapy, type of surgery, and axillary procedure. All analyses can be seen in Figure 2.

The five selected articles comprised 1,402 participants. The time to diagnosis of recurrence in the group exposed to risk factors associated with SARS was around two weeks minimum and maximum of 60 months. Figure 2 shows the estimated occurrence rate of Ras after treatment for breast cancer in the selected studies, showing that 489 (35%) of the participants developed the syndrome. Proportion = 0.35; 95% CI 0.32-0.37.

Figure 2 shows the presentation of SARS in participants who underwent chemotherapy or radiotherapy as cancer treatment. Obtaining a proportion of 39% (95% CI; 0.34-0.44) of developing SARS in the 367 who underwent chemotherapy. The 844 participants who underwent radiotherapy as oncological therapy had a proportion of 35% (95% CI; 0.31-0.38) of manifesting Ras as an outcome. Evidence of almost similar proportions of development of the syndrome, according to the total number of participants comparing one therapy to another.

Another variable analyzed was the type of surgery. Figure 2 shows the 820 participants who underwent mastectomy with and without breast reconstruction and the 582 who underwent conservative surgery,

Chart 1. Bias risk assessment (ROBINS-I)

Study	Pre-intervention		Intervention	Post-intervention				Risk of general bias
Author/year	Confusion domains	Selection	Classification of interventions	Deviation from interventions	Missing data	Outcome	Selection of reported results	
Tay et al., 2021	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Sire et al., 2020	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Ramírez-Parada et al., 2020	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Wariss et al., 2016	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟡
Moskovitz et al., 2001	🟢	🟢	🟢	🟡	🟡	🟡	🟢	🟡

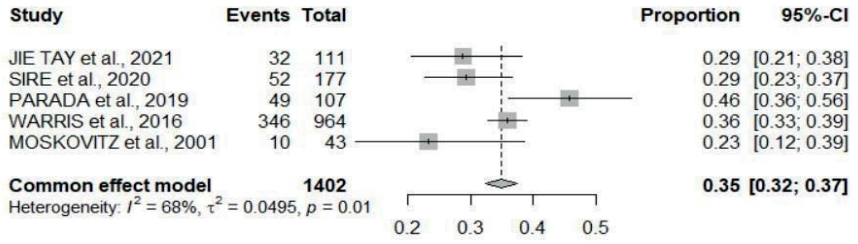
Captions: 🟢: low risk of bias; 🟡: moderate risk of bias; 🔴: high risk of bias; SI: no information.

Table 1. Characteristics and results of the selected studies

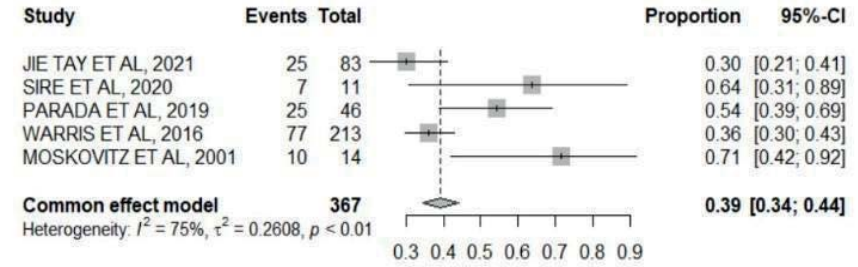
Author/ year	*Study design*	Total	Characteristics of the participants	Diagnosis, surgery, cancer treatment	RAS Assessment	With MRS	No MRS	Data Collection	Time frame for occurrence	Main associated factors	Results	Deadline for resolution of SRA or methods
Tay et al., 2021[14]	Cross-sectional, Observational	111	Asian women, undergoing surgery 2017-2019 Age: 21 years old Average: 45-50 years	CA positive, who underwent conservative surgery or mastectomy and underwent cancer treatment	Physical examination, by means of painful and visible cord palpation	32	79	Clinical and pathological data through medical records and interviews with patients	One or two years after surgery (84.8%), and 12 women (15.2%) 3 years after surgery	Age; chemotherapy; radiotherapy	Patients with SARS, who underwent Mastectomy without reconstruction and received chemotherapy and radiotherapy	High prevalence of SARS after surgery even after the acute phase, treatable with exercises and manual therapy
Sire et al., 2020[15]	Case-control study	177	Women undergoing axillary surgeries Age: medium 60.65±12.26 years)	CA positive, who underwent conservative surgery or mastectomy	Visual inspection, palpation,	52	125	Data collected from the medical records of surgeries, in the period 2018-2019	After 2 weeks of surgery	Pre-existing shoulder limitation; type of surgery; chemotherapy	Mastectomy, lymph node dissection, and chemotherapy were at increased risk	Condition that resolves spontaneously, within 3 months of onset
Ramírez--Parada et al., 2020[16]	Cross-sectional, Observational	107	Chilean women who underwent breast surgery in the period 2016-2017 Age ≥18 years Average: 56.6±51.6	evaluation of ROM, consistency of strands	Exame físico, por meio de palpação de cordão doloroso e visível, e avaliação de ADM	49	58	Data collected from medical records including number of lymph nodes removed, type of surgery, axillary procedure, chemotherapy and radiotherapy	Up to 90 days after surgery	Age; BMI; lymph node dissection	Type of surgery and lower BMI tend to be a risk for SARS and obesity is related to a lower risk of developing the syndrome	It was found that lower BMI had a higher incidence of SARS
Wariss et al., 2016[17]	Prospective cohort	964	Women diagnosed with breast CA and treated at a referral center Age: <65, average 55 years	CA positive, who have had surgery with axillary lymph node dissection or sentinel lymph node biopsy	Physical examination, by means of painful and visible cord palpation, and ROM assessment	346	618	Review of medical records, carried out in the period between 5-10 years of follow-up	Before and after surgery, 30 days, 6 months and annually up to 5 years after	Mastectomy; BMI; total lymph node dissection; chemotherapy and radiotherapy	Age, overweight, stage III or IV AC, type of surgery are associated with predisposition to SARS	ARS is a risk factor for lymphedema; active exercises, massages and manual traction can be used for regression
Moskovitz et al., 2001[18]	Retrospective observational	43	Women diagnosed with breast CA AGE: 27 YEARS OLD Average: 46	CA positive, who have had breast-conserving surgery or mastectomy with axillary lymph node dissection	Physical examination, characterized by the presence of palpable fibrous cord	11	32	Review of medical records, in the 16-year period from 1980-1996	Between 1-8 weeks after axillary surgical procedure	Mastectomy; total lymph node dissection; chemotherapy and radiotherapy	Axillary dissection is an important risk factor for SARS. Mastectomy and radiotherapy proved to be a risk factor	Non-total dissection has a lower occurrence of SARS

Captions: AC = cancer; ROM = range of motion; BMI = body mass index; Ras = axillary network syndrome.

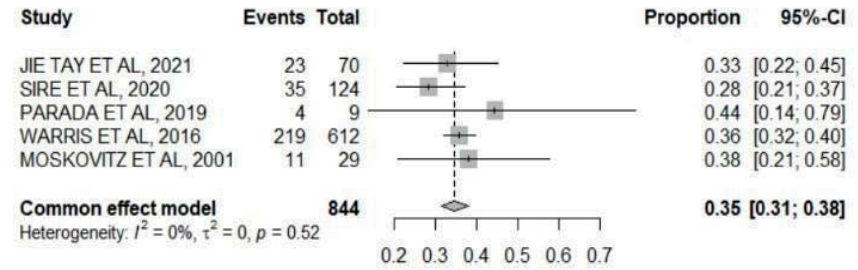
SARS occurrence rate



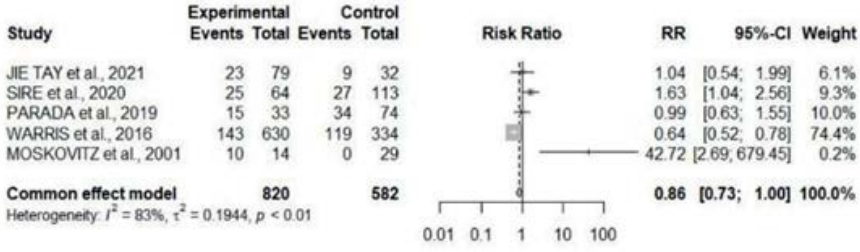
Quimioterapia



Radioterapia



Mastectomia com e sem reconstrução e Cirurgia conservadora



Procedimento axilar (Biópsia de linfonodo sentinela e Dissecção axilar)

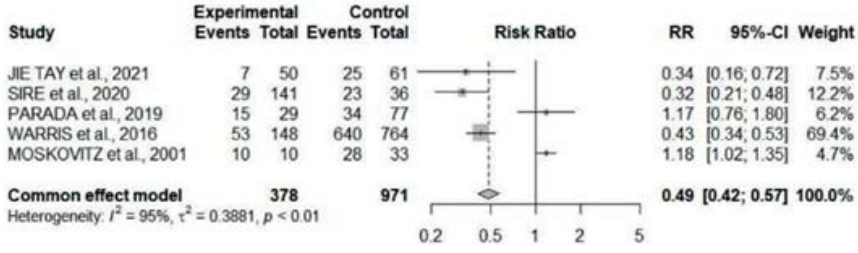


Figure 2. *Forest plot* of all outcomes assessed on the occurrence and types of therapies and interventions performed.

and it was observed that there were no statistically significant differences for Ras regardless of mastectomy or conservative surgery. Relative risk (RR) = 0.86; 95% CI; 0.73-1.00.

In addition, the type of axillary procedure was also a common analysis variable in the five selected studies. Still in Figure 2, of the 378 participants who underwent BLS, 114 developed SARS. And of the 971 participants who underwent axillary dissection, 750 developed the syndrome. Thus, it was observed that individuals who underwent BLS had a lower risk (49%) of developing Ras, compared to axillary dissection, which is a protective factor for non-triggering (RR = 0.49; 95% CI; 0.42-0.57).

In the evaluation of the GRADE system, based on the outcomes performed in the meta-analysis, in relation to structural limitations, the risk of bias was considered non-serious for the set of evidence, as it did not present methodological limitations regarding the design or execution of the studies according to the risk of general bias. The inconsistency judgment is based on the similarity of the effect estimates, the overlap of the confidence intervals and statistical criteria, such as I^2. Thus, the inconsistency of the studies was considered severe in most of the outcomes due to the great heterogeneity, ranging from 95% to 68%.

However, this is inherent in the meta-analysis of observational studies, occurring mainly because the follow-up time of the follow-ups were different, and the form of diagnosis of SARS and the results were presented differently. Indirect evidence was considered non-serious, as the outcomes evaluated were substantially based on the occurrence and factors associated with SARS, without the need to perform indirect comparisons. Inaccuracy was classified as non-serious due to the amplitude of the 95% CI and the number of events that occurred.

The publication bias was not performed due to the small number of scientific articles included in the meta-analysis. In addition, the large magnitude of the effect and the dose-response gradient did not apply to the study, but potential confounding factors, such as exclusion of patients during the study, suggested a spurious effect and, even so, this was not observed. The compositions of all outcomes examined in the meta-analysis obtained a high level of evidence in relation to the occurrence and factors associated with Ras compared to individuals who did not have the syndrome as a response (Table 2).

DISCUSSION

This systematic review with meta-analysis included five observational studies, in which the occurrence of Ras was 35% in a total of 1,402 patients involved, showing that it is present after treatment for breast cancer, and can manifest both immediately and late. This shows that SARS is a consequence that can happen routinely, secondary to breast cancer. The main associated factors found were cancer therapy performed, type of surgery and axillary procedure.

In the prospective study by Wariss et al.[17], the pathophysiology of Ras is presupposed by the discontinuation of axillary lymphatics by three mechanisms: lymphovenous injury by retraction and positioning of the patient during axillary dissection or lymphadenectomy; release of tissue factors that can cause hypercoagulation due to stasis and instability in the surrounding tissues; and by stasis of lymphovenous channels of outflow obstruction, induced by removal of axillary lymphatics that drain the arm, as well as lymphedema, in which the pathophysiology is described by disruption of the lymphatic system, resulting in decreased lymphatic flow.

The retrospective study by Tay et al.[14] ensured that women who underwent surgery are at risk of developing SARS, with an occurrence of 28.9% in the 111 women evaluated, among whom the majority had the syndrome one or two years after surgery (84.8%), and 12 patients (15.2%) had it three years after surgery. A prospective cohort study by Koehler et al.[19] with 36 patients obtained a cumulative prevalence of 50% of Ras at 18 months after surgery, while another prospective cohort study by O' Toole et al.[20] found an incidence of 31.5% at 24 months postoperatively, which states that Ras may present as a late complication. This may be due to the failure of the investigation by the patients and the lack of constant and vile monitoring, due to the ignorance of the condition[14].

In the case-control study by Sire et al.[15], the 177 women evaluated had an occurrence of 29.5% of Ras within two weeks postoperatively. The most frequent location was in the axillary level (59.6%), arm (17.3%), in the cubital fossa (11.5%) and in the forearm (11.5%), showing that Ras is more present in the region where the lymph nodes are removed and less common during its course.

It was observed that, in the meta-analysis in question, there was an occurrence of 39% of Ras in patients who underwent chemotherapy as an adjuvant treatment. In the retrospective study by Jeong et al.[21], 189 eligible patients were recruited and underwent surgery between 2019 and 2020, of which 117 (62%) underwent chemotherapy, with 25 (43.10%) patients having SARS as an outcome. The study by Bergmann et al.[22] had 193 women who underwent neoadjuvant chemotherapy and radiotherapy, and pointed out that there was no increase in the risk of development, with only 17 individuals who manifested

Table 2. GRID system applied in the selected studies

Certainty assessment							Nº. of patients		Effect		*Certainty*
Nº of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirect evidence**	**Fuzziness**	**Other considerations**	**Prevalence and risk factors associated with the occurrence of SARS**	**Individuals who did not present the outcome of SARS**	**Relative (95% CI)**	**Absolute (95% CI)**	
Evaluation of the occurrence of SARS in patients undergoing treatment for breast cancer (follow-up: range 3 weeks to 10 years)											
5	Observational study.	Not serious	Record[a]	Not serious	Not serious	All potential confounding factors would suggest a spurious effect, and even then, no effect was observed	489/1402 (34.9%)	913/1402 (65.1%)	Uncombined		⊕⊕⊕⊕ High
Axillary procedure (sentinel lymph node biopsy or axillary dissection)											
5	Observational study.	Not serious	Record[a]	Not serious	Not serious	All potential confounding factors would suggest a spurious effect, and even then, no effect was observed	99/378 (26.2%)	750/971 (77.2%)	RR 0.49 (0.42 to 0.57)	394 less per mil (from 448 less to 332 less)	⊕⊕⊕⊕ High
Type of Surgery (mastectomy with and without reconstruction compared to conservative surgery)											
5	Observational study.	Not serious	Record[a]	Not serious	Not serious	All potential confounding factors would suggest a spurious effect, and even then, no effect was observed	216/820 (26.3%)	189/582 (32.5%)	RR 0.86 (0.73 to 1.00)	45 less per thousand (from 88 less to 0 less)	⊕⊕⊕⊕ High
Chemotherapy and Ras											
5	Observational study.	Not serious	Record[a]	Not serious	Not serious	All potential confounding factors would suggest a spurious effect, and even then, no effect was observed	144/367 (39.2%)	223/367 (60.8%)	Uncombined		⊕⊕⊕⊕ High
Radiotherapy and Ras											
5	Observational study.	Not serious	Not serious	Not serious	Not serious	All potential confounding factors suggested a spurious effect, and even then, no effect was observed	292/844 (34.6%)	552/844 (65.4%)	Uncombined		⊕⊕⊕⊕ High

Captions: SARS = axillary network syndrome; CI = confidence interval; RR = hazard ratio.
(a) All meta-analyses showed high heterogeneity, although this is inherent in meta-analyses of observational studies.

SARS. However, in the control case of Sire et al.[15], of the 177 women who underwent surgery, 11 used neoadjuvant chemotherapy and 57 used taxane chemotherapy, and had a higher risk of developing SARS, with 13.5% and 46.1%, respectively.

In contrast, in the retrospective study by Moskovitz et al.[18], among the 43 women evaluated, of the 14 who underwent chemotherapy, ten had SARS. Hassan et al.[23] state in their review that the main objective of systemic adjuvant treatment is to control any micro metastatic disease, reduce the recurrence rate and improve overall long-term survival. In addition, in the retrospective study by Chou et al.[24] with a total of 173 patients, the incidence of Ras was 18%, with a predominant difference in age (p=0.004), number of lymph nodes removed (p=0.044), and whether they were receiving chemotherapy (p=0.002) between patients with and without the syndrome. These three factors have been associated with an increased risk of developing SARS, evidence that chemotherapy may be an isolated or combined risk factor.

The meta-analysis shows that 35% of patients who underwent radiotherapy as cancer treatment had SARS as an outcome. Hennequin et al.[25] report that, after surgery for infiltrating carcinoma, radiotherapy should be performed systematically, regardless of the characteristics of the disease, as it decreases the local recurrence rate and, therefore, mortality.

In the cross-sectional study by Tay et al.[14], 59.5% of the 111 patients who received radiotherapy had SARS. In the prospective cohort study by Bergmann et al.[22] with 193 women, 52 underwent radiotherapy as cancer treatment, of which only two participants had Ras, showing that this factor did not increase the risk of development. Fukushima et al.[26] carried out a cross-sectional observational study with 97 women over 18 years of age, between 2011 and 2012, in which 28 participants presented Ras, of which only three had undergone radiotherapy as oncological treatment, distinguishing that this is not a risk factor that necessarily causes the pathology in question.

On the other hand, the cross-sectional study by Ramirez-Parada et al.[16] reports the incidence of SARS in 107 patients, of whom nine underwent radiotherapy, four of whom had the syndrome as a consequence, with a relatively high prevalence in relation to the total number, but the small number of participants included in the study who underwent this treatment alone should be considered. Comparing the two types of cancer treatments used in breast cancer, the proportions of RAS appearance obtained in the meta-analysis are relatively similar, ranging from 35% to 39%, showing that the signs and symptoms of the disease can occur regardless of the therapy used to address breast cancer.

In addition, the meta-analysis addresses that Ras can develop regardless of the type of surgical approach performed. Surgery is classified as the primary treatment for breast cancer[1,27]. The classification consists of simple mastectomy, modified radical, skin and nipple sparing[27,28]. Conservative surgery has become the elective alternative in the treatment of breast cancer, however, to achieve free margins of neoplasms and reduce the risk of local recurrence, in case of large lesions, the procedure can often compromise the aesthetic result, for small breasts or resection of more than 30% of the breast volume. The advantages of using conservative surgical techniques are preservation of most of the breast parenchyma, reduction of morbidity, and reduction of surgical impact on its functioning[19,27,29].

In the observational study by Tay et al.[14], of the 111 women evaluated, 79 underwent mastectomy, 23 (30%) presented SARS, compared to the 32 participants who underwent conservative surgery, and only nine (27.9%) developed SARS, indicating that, regardless of the type of surgery performed, the patients presented similar proportions of triggering. In the case-control study by Sire et al.[15], 177 patients were recruited, of the 64 who underwent mastectomy, 48.1% developed SARS and, among the 113 who succeeded by conservative surgery, 51.9% presented SARS as the outcome, both results within two weeks postoperatively, also showing that SARS can appear in both types of surgical procedures.

However, in the retrospective study by Moskovitz et al.[18], women who underwent conservative surgery did not present SARS as an outcome, but the small number of participants included should be considered and this was the first study to verify the prevalence of SARS in women with breast cancer.

The surgical procedure associated with lymph node chain dissection may influence the reported frequency of Ras, as this approach is more aggressive than BLS, as can be evidenced in the meta-analysis, with lower occurrence of Ras (49%) in BLS compared to axillary lymph node dissection. Anatomically, the axillary lymph nodes are divided into three levels, with the pectoralis minor muscle as the demarcation. The lymph nodes located lateral to the pectoralis minor are level I axillaries, which include the lateral mammary group, the central group, and the subscapular group; those located posterior to the deep surface of the pectoralis minor are level II; and those located medial to the pectoralis minor are level III[30,31].

Axillary lymph node dissection levels I and II is the optimal clinical treatment of axillary lymph node positive breast cancer. Level III dissection can lead to postoperative numbness, axillary deformity, lymphedema, SARS, etc. As a result, BLS has a profound effect on reducing axillary

trauma by causing less lymph node injury. In most cases, BLS replaced axillary dissection in patients with clinically negative lymph nodes[21,30,31].

In the cross-sectional study by Tay et al.[14], among the 61 patients who underwent lymph node dissection, there were 25 (41.0%) with development of SARS and, of the 50 who underwent BLS, only seven (14%) developed SARS. The increased risk of Ras associated with axillary dissection is due to the fact that it is a more invasive surgical intervention, in which there is a risk of disruption of axillary lymphatics or thrombosed lymphatic vessels, causing fibrosis at the site. In addition, the case-control study by Sire et al.[15] evaluated 141 participants who underwent BLS, with 29 (21%) positive for SARS, and of the 36 who underwent axillary dissection, 23 (64%) developed the syndrome, showing that axillary dissection is an important risk factor for the development of SARS.

The study presents limitations regarding the difficulty to obtain a homogeneous sample in relation to the follow-up time and the methodological deficiency of the articles because they bring different and not so clarified forms in the description of the results obtained. Thus, future studies are suggested for the more detailed investigation of SARS, and its evasion methods and techniques, requiring more current research in this target audience.

CONCLUSION

Thus, it was observed that individuals undergoing treatment for breast cancer have a 35% occurrence rate of developing SARS both acutely and late. These findings suggest that patients undergoing BLS have a lower risk of having the syndrome compared to lymph node dissection. The type of cancer treatment – chemotherapy or radiotherapy – shows almost equivalent results, 39% and 35% for triggering, and both mastectomy and conservative surgery obtain results that are not statistically significant for SARS.

CONTRIBUTIONS

All authors contributed at all stages of the article and approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

FUNDING SOURCES

None.

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Recebido em 28/3/2023
Aprovado em 26/6/2023

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