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CAMILA MELO MESQUITA

ANÁLISE DO PAPEL DO ÍNDICE DE IMUNO-INFLAMAÇÃO SISTÊMICA COMO FATOR DE PROGNÓSTICO NO CÂNCER DE MAMA TRIPLO NEGATIVO

SOBRAL-CE
2023

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Dissertação apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal do Ceará-Campus Sobral como requisito necessário para obtenção do título de Mestre em Ciências da Saúde.
Linha de pesquisa: Doenças Crônicas e Câncer
Área temática: Neoplasias benignas e malignas da cavidade oral
Orientador: Prof. Dr. Filipe Nobre Chaves

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“Tudo posso naquele que me fortalece”

Filipenses 4:13

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RESUMO

O câncer de mama é a neoplasia mais incidente entre pacientes do sexo feminino, como também a primeira causa de morte em todas as regiões brasileiras, exceto a região Norte. O prognóstico desse tipo de câncer dependerá de determinados aspectos, como a classificação molecular, sendo o tipo triplo negativo a modalidade mais agressiva. Dessa forma, alguns biomarcadores têm sido utilizados como fatores para a avaliação da sobrevida global do câncer de mama, como o Ki-67, carga residual do câncer e, atualmente, as células do sistema imunológico e inflamatório do hospedeiro são consideradas "peças-chave" para a avaliação do prognóstico, como neutrófilos, linfócitos e plaquetas. É importante ressaltar que essa avaliação ocorrerá por meio do Índice de Imuno-Inflamação Sistêmica (SII) que é considerado um parâmetro hematológico abrangente. Dessa forma, a presente dissertação por um capítulo que tem como objetivo geral analisar a relação entre o índice de SII como prognóstico de pacientes com câncer de mama triplo negativo, e como objetivos específicos: 1) Realizar uma revisão sistemática com metanálise; 2) Correlacionar a Sobrevida Global (OS) e Sobrevida Livre da Doença (DFS) com SII em pacientes com câncer de mama triplo negativo; 3) Avaliar as características demográficas e clínico-patológicas. No capítulo 1, realizou-se uma revisão sistemática com metanálise registrada na base de dados PROPERO. A estratégia de busca foi realizada em seis bases de dados, incluindo a literatura cinzenta. Após a aplicação de todos os critérios de elegibilidade 03 estudos foram selecionados. Foram avaliados os desfechos de Sobrevida Global e Sobrevida Livre da Doença, sugerindo que o SII é um indicador promissor para o prognóstico de câncer de mama triplo negativo. Porém, ainda há necessidade da realização de mais estudos acerca da temática.

Palavras-chave: Câncer de Mama; Índice de Imuno-Inflamação Sistêmica; Epidemiologia; Metanálise; Revisão Sistemática

ABSTRACT

Breast cancer is the most frequent neoplasm among female patients, as well as the first cause of death in all Brazilian regions, except the North region. The prognosis of this type of cancer will depend on certain aspects, such as the molecular classification, with the triple negative type being the most aggressive modality. Thus, some biomarkers have been used as factors for the assessment of overall breast cancer survival, such as Ki-67, residual cancer burden and, currently, host immune and inflammatory cells are considered “key parts ” for the evaluation of prognosis, such as neutrophils, lymphocytes and platelets. It is important to point out that this evaluation will take place through the Systemic Immuno-Inflammation Index (SII), which is considered a comprehensive hematological parameter. Thus, this dissertation comprises a chapter that has the general objective of analyzing the relationship between the IBS index as a prognosis for patients with triple negative breast cancer, and the specific objectives: 1) Carry out a systematic review with meta-analysis; 2) Correlate Overall Survival (OS) and Disease Free Survival (DFS) with IBS in patients with triple negative breast cancer; 3) Evaluate the demographic and clinical-pathological characteristics. In chapter 1, a systematic review was carried out with a meta-analysis recorded in the PROPERO database. The search strategy was performed on six databases, including the gray literature. After applying all eligibility criteria, 03 studies were selected. The outcomes of Overall Survival and Disease Free Survival were evaluated, suggesting that IBS is a promising indicator for the prognosis of triple negative breast cancer. However, there is still a need for further studies on the subject.

Key-words: Breast cancer; Systemic Immuno-Inflammation Index; Epidemiology; Meta-analysis; Systematic review.

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LISTA DE ABREVIATURA E SIGLAS

ER	Do inglês *Estrogen Receptor*
PR	Do inglês *Progesterone Receptor*
HER2	Do inglês *Human Epidermal Growth Factor Type 2*
SII	Do inglês *Systemic Immune-Inflammation Index*
CTC	Células Tumorais Circulantes
VEGF	Do inglês *Vascular Endothelial Growth Factor*
P	Do inglês *Platelets*
N	Do inglês *Neutrophils*
L	Do inglês *Lymphocytes*
TNBC	Do inglês *Triple Negative Breast Cancer*
OS	Do inglês *Overall Survival*
DFS	Do inglês *Disease-Free Survival*
DMFS	Do inglês *Distant Free Metastasis Survival*
DSS	Do inglês *Disease Specific Survival*
NLR	Do inglês *Neutrophils and Lymphocytes Ratio*
LMR	Do inglês *Lymphocyte-to-Monocyte Ratio*
PRL	Do inglês *Platelets-Lymphocytes Ratio*

SUMÁRIO

1 INTRODUÇÃO GERAL

CÂNCER DE MAMA

O câncer de mama é a multiplicação desordenada de células anormais no tecido mamário, formando o tumor que poderá apresentar potencial invasivo a outros tecidos. Além disso, apresenta alterações clínicas características como edema mamário localizado ou em toda a mama, inversão do mamilo, eritema na pele, secreção serosa ou sanguinolenta por um dos mamilos e linfonodos infartados (YEO, 2017; BONILLA, 2017).

De acordo com dados com INCA 2022, o câncer de mama é o mais incidente em mulheres no mundo, com aproximadamente 2,3 milhões de caos novos estimados para o biênio 2020-2022, representando 24,5% de casos novos por câncer em mulheres. No Brasil, excluindo os tumores de pele não melanoma, é o tipo de câncer mais incidente em mulheres de todas as regiões. São estimados 704 mil novos casos para o triênio 2023-2025, e 70% desses casos são previstos para as regiões Sul e Sudeste.

De acordo com o Ministério da Saúde (2019), a idade é considerada o principal fator de risco para o câncer de mama feminino. As taxas de incidência aumentam consideravelmente até os 50 anos. Além disso, eventos relacionados à vida reprodutiva da mulher também são considerados como fatores de risco, histórico familiar de câncer de mama, obesidade, dentre outros. Entretanto, nos pacientes do sexo masculino, o aumento da incidência ocorre tardiamente, por volta dos 70 anos. Devido à raridade do câncer de mama masculino, não é possível uma análise fidedigna de quais são seus fatores de risco (ANDERSON et al., 2017).

As opções de tratamento do câncer de mama incluem: remoção cirúrgica do tumor primário, avaliação do acometimento axilar e radioterapia como formas de tratamento local. Com relação as formas de tratamento sistêmico estão disponíveis a quimioterapia e a hormonoterapia. A quimioterapia realizada posteriormente à intervenção local é chamada de adjuvante. Quando realizada antes da cirurgia curativa, é denominada de neoadjuvante que recebe destaque e vem sendo amplamente aceita por possibilitar o aumento da sobrevida do paciente, pois tem como principais objetivos eliminar possíveis metástases, promover a redução do tumor para que assim possa possibilitar um melhor resultado cirúrgico, além de avaliar a sensibilidade do tumor para o tratamento sistêmico (CORTAZAR, 2015; MS, 2019).

A escolha das medicações utilizadas no planejamento terapêutico da quimioterapia antineoplásica, bem como o prognóstico dependerá da classificação do subtipo molecular do tumor. Essa classificação terá como base os marcadores de proliferação, o grau histológico, a

presença de receptores de estrogênio (ER) e progesterona (PR) e a expressão do fator de crescimento epidérmico humano 2 (HER2). A maioria dos estudos subdividem a classificação molecular em: luminal A que possui melhor prognóstico, com altas taxas de sobrevivência e baixas taxas de recorrência, apresentam receptores de estrogênio e progesterona, por isso inclui a hormonoterapia na sua forma de tratamento, e HER2 negativo; luminal B possui o prognóstico mais incerto se comparado ao luminal A, pois pacientes com esse subtipo são normalmente diagnosticadas com tumores em estágios mais avançados. É caracterizado por expressar receptores de estrogênio e/ou progesterona positivos e HER2 positivo ou negativo; triplo negativo é mais comum em mulheres jovens e com descendência africana. Nesse não será verificado a presença RE e RP, e ausência da expressão de HER2; e HER2-positivo em que há superexpressão de HER2 e ausência dos receptores hormonais RE e RP (BARRETO NETO, 2014; FISUSI, 2019).

Alguns tipos de biomarcadores têm sido utilizados como fatores para a avaliação da sobrevida global do câncer de mama, como o Ki-67, carga residual do câncer e, atualmente, as células do sistema imunológico e inflamatório do hospedeiro são consideradas “peças-chave” para a avaliação do prognóstico, como neutrófilos, linfócitos e plaquetas. É importante ressaltar que essa avaliação ocorrerá por meio do Índice de Imuno-Inflamação Sistêmica (SII) que é considerado um parâmetro hematológico abrangente (AZIZ, 2019; JIANG, 2020).

ÍNDICE DE IMUNO-INFLAMAÇÃO SISTÊMICA

O SII foi desenvolvido e utilizado pela primeira vez como método de avaliação no carcinoma hepatocelular por Hu et al (2014) que o definiu um indicador integrado baseado na contagem de plaquetas, linfócitos e neutrófilos, tendo a função de melhor prever o equilíbrio entre o estado inflamatório e imunológico do hospedeiro, podendo assim ser utilizado como um dos possíveis marcadores a respeito do prognóstico do câncer.

Sua elaboração foi baseada na possibilidade da disseminação hematogênica das Células Tumorais Circulantes (CTC) que desempenham papel importante na formação de metástase. Além disso, células imunes e inflamatórias contribuem para a disseminação e invasão tumoral, como as plaquetas que protegem as CTC’s das tensões de cisalhamento durante a circulação, auxiliam na transição epitelial-mesenquimal e permitem o extravasamento de CTC’s para locais metastáticos; os neutrófilos por sua vez, através da secreção de fatores de crescimento circulantes como o Fator de Crescimento Endotelial Vascular (VEGF) e proteases, promovem a adesão e semeadura das CTC’s; e os linfócitos ditarão a resposta imune do hospedeiro à

malignidade, haja vista que serão responsáveis pela morte células citotóxica e inibindo a proliferação e migração das células tumorais. Sendo assim, o seu cálculo foi descrito da seguinte maneira: SII= P x N/L, onde P, N e L são plaquetas, neutrófilos e linfócitos, respectivamente (AZIZ, 2018; LI, 2019; HU, 2014).

O SII foi utilizado pela primeira vez no câncer de mama por Willik et al (2018) em que foram comparados índices inflamatórios entre mulheres sobreviventes do câncer de mama que receberam quimioterapia adjuvante com mulheres livres de câncer de mama e que nunca haviam recebido qualquer tipo de quimioterapia. O estado inflamatório foi avaliado por meio da razão granulócitos para linfócitos, relação plaqueta-linfócito e SII. Como resultado foi observado que ocorre o aumento dos índices inflamatórios, mesmo após o tratamento quimioterápico.

O estudo de Liu et al (2019) foi o primeiro a investigar a associação entre SII e prognóstico do câncer de mama triplo negativo (TNBC). Nessa pesquisa a análise dos níveis de SII pré-tratamento e sobrevida do paciente. Dessa forma, foi observado na amostra avaliada que o SII pode ter valor significativo como prognóstico independente em pacientes com TNBC.

Apesar de ser utilizado como ferramenta para a análise do prognóstico de cânceres como o colorretal, nasofaríngeo, pancreático e próstata. Ainda não há uma total compreensão do seu papel com relação ao câncer de mama. É importante destacar a baixa quantidade de estudos na literatura que avaliem o papel do SII como fator de prognóstico independente para o TNBC.

2 PROPOSIÇÃO GERAL

Geral

Analisar a relação entre o índice de SII como prognóstico de pacientes com TNBC.

Específicos

- Realizar uma revisão sistemática com metanálise no PROSPERO para avaliar o SII como prognóstico em pacientes com TNBC.
- Correlacionar a Sobrevida Global (OS) e Sobrevida Livre da Doença (DFS) com SII em pacientes com TNBC.
- Avaliar as características demográficas e clínico-patológicas das pacientes.

3 CAPÍTULO ÚNICO

A presente dissertação de Mestrado está baseada no Artigo 43 do Regimento Interno do Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal do Ceará que regulamenta o formato alternativo para dissertação de Mestrado e permite a inserção de artigos científicos de autoria ou coautotia do candidato (ANEXO). Assim sendo, esta dissertação é composta de um capítulo contendo um artigo científico que foi submetido ao periódico "***Clinical Breast Cancer"***.

3.1 Capítulo Único: ÍNDICE DE IMUNO-INFLAMAÇÃO SISTÊMICA COMO FATOR PARA O PROGNÓSTICO DO CÂNCER DE MAMA TRIPLO NEGATIVO: REVISÃO SISTEMÁTICA COM METANÁLISE

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ÍNDICE DE IMUNO-INFLAMAÇÃO SISTÊMICA COMO FATOR PARA O PROGNÓSTICO DO CÂNCER DE MAMA TRIPLO NEGATIVO: REVISÃO SISTEMÁTICA COM METANÁLISE

RESUMO

O Índice de Imuno-Inflamação Sistêmica (SII) vem sendo considerado um marcador hematológico promissor que permite avaliar de forma integrada o equilíbrio entre o sistema inflamatório e imunológico de pacientes com câncer. Apesar de ser utilizado como fator de prognóstico independente para alguns tipos de cânceres como o nasofaríngeo, colorretal, pâncreas e hepático, ainda há poucos estudos que correlacionem o valor de SII com o prognóstico do câncer de mama, principalmente o triplo negativo que é caracterizado por apresentar comportamento agressivo. Sendo assim, o presente estudo buscou identificar, através de uma metanálise, aspectos clinico-patológicos e o valor do prognóstico de SII em pacientes com câncer de mama triplo negativo. Dessa forma, realizamos uma pesquisa bibliográfica nas seguintes bases de dados: PubMed, Embase, Scopus e Web of Science, Livivo e Google Scholar. Como critérios de inclusão foram considerados artigos que fossem publicados até o ano de 2023, não houve restrições com relação ao idioma de publicação, estudos primários que abordassem a relação entre SII e o prognóstico de pacientes com câncer de mama triplo negativo, tendo como desfechos a Sobrevida Global (OS) e Sobrevida Livre da Doença (DFS). Foram excluídos revisões de literatura, séries e relatos de casos, estudos duplicados, estudos em animal e com dados insuficientes. O valor do prognóstico foi estimado através de *Hazard Ratio* (HR) e Risco Relativo com Intervalo de Confiança (IC) de 95%. Sendo assim, três estudos obedeceram aos critérios de elegibilidade, totalizando 499 pacientes avaliados. Os resultados da metanálise multivariada mostraram que SII elevado é fator de prognóstico para OS e DFS: [HR (análise univariada) = 2,41 (1,23-4,71), p=0,01); HR (análise multivariada) = 2,82 (2,22-3,59), p<0,01] e [HR (análise univariada) = 2,41 (1,45-4,01), p<0,01; HR (análise multivariada) = 2,02 (1,05-3,89), p=0,04], respectivamente. Apesar de nosso estudo mostrar que SII é um indicador promissor para o prognóstico no TNBC, ainda há necessidade da realização de mais estudos acerca da temática.

Palavras-chave: Triplo Negativo; Neoplasia de Mama; Prognóstico; Índice de Imuno-Inflamação Sistêmica**.**

ABSTRACT

The Systemic Immune-Inflammation Index has been considered a promising hematological marker that allows an integrated assessment of the balance between the inflammatory and immune systems in cancer patients. Despite being used as an independent prognostic factor for some types of cancer such as nasopharyngeal, colorectal, pancreas and liver, there are still few studies that correlate the SII value with the prognosis of breast cancer, especially the triple negative that is characterized by exhibit aggressive behavior. Therefore, the present study sought to identify, through a meta-analysis, clinicopathological aspects and the prognostic value of Systematic Immune-Inflammation in patients with triple negative breast cancer. Thus, we performed a bibliographical research in the following databases: PubMed, Embase, Scopus and Web of Science, Livivo and Google Scholar. As inclusion criteria, we considered articles that were published until the year of 2023, there were no restrictions regarding the language of publication, primary studies that addressed the relationship between Systemic Immune-Inflammation Index and the prognosis of patients with triple negative breast cancer, with the outcomes being Overall Survival and Disease Free Survival. Literature reviews, series and case reports, duplicate studies, animal studies and studies with insufficient data were excluded. The prognostic value was estimated using Hazard Ratio (HR) and Relative Risk with a Confidence Interval of 95%. Thus, three studies met the eligibility criteria, totaling 499 patients evaluated. The results of the multivariate meta-analysis showed that high SII is a prognostic factor for Overall Survival and Disease Free Survival: [HR (univariate analysis) = 2.41 (1.23-4.71), p=0.01); HR (multivariate analysis) = 2.82 (2.22-3.59), p<0.01] and [HR (univariate analysis) = 2.41 (1.45-4.01), p<0, 01; HR (multivariate analysis) = 2.02 (1.05-3.89), p=0.04], respectively. Although our study shows that IBS is a promising indicator for prognosis in TNBC, there is still a need for further studies on the subject.

Key-words: Triple Negative, Breast Neoplasms, Prognosis, Systemic Immune-Inflammation Index

INTRODUÇÃO

O câncer de mama triplo negativo (TNBC) é o subtipo molecular em que é verificada a ausência de receptores hormonais de estrógeno e progesterona (PR e ER), além da ausência do fator de crescimento epidérmico humano tipo 2 (HER2), o que dificulta o uso da terapia direcionada. Esse subtipo representa aproximadamente 15% dos tumores de mama, ocorrendo com maior frequência em mulheres jovens, abaixo de 40 anos, negras e hispânicas[1-3]. Além disso, é caracterizado por apresentar alta taxa de recorrência, principalmente nos primeiros 3 a 5 anos após o diagnóstico, reduzindo consequentemente o tempo de sobrevida[4.]

Nesse contexto, pesquisas têm buscado investigar o papel de biomarcadores prognóstico no TNBC. Dentre eles, alguns estudos têm investigado o papel de marcadores hematológico na sobrevida de pacientes com TNBC. Vale destacar que o microambiente inflamatório favorecerá o desenvolvimento e progressão do câncer, de modo que, a sua redução irá influenciar diretamente no êxito do tratamento. Dessa forma, são estabelecidos como biomarcadores inflamatórios o número de linfócitos, neutrófilos e plaquetas, utilizando-se a razão neutrófilos e linfócitos (NLR), a razão monócitos e linfócito (MLR) e a razão plaquetas e linfócitos (PLR)[5-7].

Outro parâmetro que vem sendo muito utilizado é o índice de imuno-inflamação sistêmica (SII). Tal índice consiste em um indicador integrado baseado na contagem de plaquetas, linfócitos e neutrófilos (NxP/L), apresentando uma melhor eficácia na avaliação do equilíbrio entre o estado inflamatório e imunológico do hospedeiro. Apesar do SII ter sido investigado em tumores sólidos como a câncer de pâncreas, fígado e estômago, ainda há poucos estudos que o avalie como preditor no prognóstico do TNBC[8].

Por conseguinte, a presente revisão sistemática buscou investigar a associação entre o SII e o prognóstico de pacientes com TNBC e avaliar a certeza da evidência gerada.

METODOLOGIA

Para o relato da presente pesquisa utilizamos como base o *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA)[9]. Além disso, o estudo foi cadastrado na *International Prospective Register of Systematic Reviews* (PROSPERO), com o número CRD42022382950.

Critérios de Elegibilidade

A pergunta norteadora para a elaboração dessa revisão foi: Existe associação entre o SII e o prognóstico de pacientes com câncer de mama triplo negativo? Desta forma, foram adotados os seguintes critérios de inclusão: estudos que avaliaram a relação entre o SII e o prognóstico do TNBC por OS ou DFS. Vale ressaltar que não restringimos o período de publicação, nem idioma. Os critérios de exclusão consistiram em: estudos de revisão e relato de caso; estudos realizados em modelo animal ou *in vitro*; estudos duplicados; e os estudos que não reportaram *Hazard Ratio* (HR), nem intervalo de confiança (IC).

Fontes de Informação

Realizou-se as buscas nas seguintes bases de dados: PubMed, Embase, Web of Science, Livivo, Scopus e Google Scholar (para identificação da literatura cinzenta). Para o gerenciamento das referências e exclusão de estudos duplicados utilizamos como ferramenta o EndNote e o Rayyan [10]. As buscas foram realizadas em 12 de dezembro de 2022.

Estratégia de Busca

Para a elaboração das estratégias de busca foram utilizados os seguintes descritores: "*Triple Negative Breast Neoplasms"; "Prognosis"; "Systemic Immune-Inflammation Index".* Utilizamos também termos semelhantes e os operadores booleanos "AND" e "OR". Para mais detalhes sobre a estratégia utilizada em cada base de dados consulte a tabela suplementar 1.

Seleção dos Estudos

O processo de seleção dos estudos foi realizado em duas fases. A primeira fase consistiu na leitura de títulos e resumos. A segunda fase compreendeu a leitura de texto completo dos estudos. Todas as fases do processo de seleção foram realizadas por dois revisores (CMM, JDLF). É importante ressaltar que um terceiro revisor (DFGO) contribuiu para solucionar os casos de discordância entre os autores. Vale destacar, que utilizamos o software Rayyan para o gerenciamento das duas fases do processo de seleção.

Processo de Coleta de Dados

O processo de coleta de dados foi realizado por dois autores de forma independente (CMM, JDLF). Nos casos de discordância, o consenso foi decidido através do auxílio de um terceiro revisor (DFGO). Para a coleta de dados foi elaborada uma planilha no *Google Sheets*. Os dados coletados foram: ano, país, continente, tipo de estudo, amostra (TNBC), idade, sexo,

diferenciação tumoral, tipo histológico, classificação TNM, estágio clínico, tipo de cirurgia (cirurgia conservadora e mastectomia radical), quimioterapia (adjuvante e neoadjuvante), radioterapia (adjuvante e neoadjuvante), SII (alto e baixo), *cut off*, momento da avaliação do SII, tempo de *follow up*, dados para quais desfechos, HR e intervalo de confiança (OS, Sobrevida Específica da Doença-DSS e DFS).

Avaliação do Risco de Viés

A avaliação do risco de viés nos estudos incluídos foi realizada com o checklist de avaliação crítica para estudos de coorte do Instituto Joanna Briggs[11]. Este formulário é constituído pelas seguintes questões: Q1) Os dois grupos eram semelhantes e recrutados a partir da mesma população? Q2) As exposições foram medidas de forma semelhante para designar as pessoas a grupos expostos e não expostos? Q3) A exposição foi medida de forma válida e confiável? Q4) Foram identificados fatores de confusão? Q5) Foram estabelecidas estratégias para lidar com fatores de confusão? Q6) Os grupos / participantes estavam livres do desfecho no início do estudo (ou no momento da exposição)? Q7) Os resultados foram medidos de forma válida e confiável? Q8) O tempo de *follow up* foi relatado e suficiente para que os resultados ocorressem? Q9) O *follow up* foi completo e, em caso negativo, as razões para a perda de acompanhamento foram descritas e exploradas? Q10) Foram utilizadas estratégias para abordar o *follow up* incompleto? Q11) Foi usada análise estatística apropriada? Vale apontar que a avaliação foi realizada por dois revisores (CMM, JDLF), sendo que o consenso foi empreendido por um terceiro revisor (DFGO).

Para classificar o risco geral de viés de cada estudo, utilizamos o percentual de "sim" recebido no checklist. Dessa forma, adotou-se a seguinte classificação: o estudo foi considerado como apresentando alto risco de viés em caso de percentual menor que 50%; estudo com risco moderado de viés no caso de percentual de 50 a menor que 70%; e baixo risco de viés para percentual igual ou maior que 70%. É importante destacar, que esses pontos de cortes foram adotados com base em estudos de revisões sistemáticas que também utilizaram checklists do Instituto Joanna Briggs[12-13]. Ressalta-se que a figura de risco de viés foi gerada com o software R na versão 4.0.5 (pacote dmetar).

Medidas de Efeito e Síntese dos Resultados

Os desfechos avaliados nesta revisão foram a OS e DFS. Por conseguinte, utilizou-se o HR como medida de efeito. Assim, empregou-se metanálises para agrupar o HR na forma de logaritmo natural e respectivo erro padrão, através do software estatístico R (versão 4.0.5,

pacote meta). Para as análises, adotou-se o modelo randômico visto que os estudos eram provenientes de populações diferentes, e aplicou-se o método do inverso da variância. I^2 e o teste Q foram utilizados para investigar a heterogeneidade estatística entre os estudos. Vale destacar que adotamos um nível de significância de 5% para todas as análises ($p < 0,05$).

Avaliação da Certeza da Evidência

A avaliação da certeza da evidência foi realizada pelo *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) [14]. Os critérios considerados neste sistema de classificação são os seguintes: risco de viés, inconsistência, imprecisão, presença de evidência indireta e o viés de publicação. Destaca-se que nos estudos observacionais a certeza da evidência inicia como sendo baixa podendo diminuir de nível a partir dos critérios supracitados, ou subir de nível nos seguintes casos: efeito de grande magnitude, presença de efeito dose-resposta, ou ainda em casos de efeitos confundidores contrários à medida de efeito. Salienta-se que a avaliação da certeza da evidência foi realizada utilizando software GRADEpro online (*McMaster University and Evidence Prime Inc*.).

RESULTADOS

Seleção dos Estudos

Durante a busca de dados foram identificados 391 estudos na literatura (veja figura 1). Desses, 128 eram duplicados. Em seguida, 263 estudos foram avaliados na fase 1 da seleção, sendo que 247 foram excluídos. Por conseguinte, 16 estudos foram analisados na fase 2. Desses, 3 estudos obedeceram aos critérios de elegibilidade. No total foram excluídos 9 estudos nessa fase devido aos seguintes motivos: estudos que não apresentavam os desfechos de interesse (5); que não apresentavam dados de HR (3) e estudo não publicado em alfabeto romano (1).

Características dos Estudos

No total, 3 estudos foram incluídos nesta revisão, tendo sido realizados nos Estados Unidos (1) e China (2). Os mesmos foram publicados no ano de 2019 (veja tabela 1). Todos os estudos eram do tipo coorte retrospectiva. Vale destacar que apenas Liu et al., 2019 e Wang et al., 2019 demostram as características clínicas dos pacientes com TNBC. Tais características foram agrupadas por metanálises e podem ser consultadas na tabela 2. Como podemos perceber o follow-up médio dessas pacientes foram de 61,87 meses, sendo mais comum tumores pT2

(58,13%). Com relação ao envolvimento de linfonodos, foi observado uma maior proporção de casos pN0 (42,38%). Vale ressaltar que observamos que o carcinoma ductal invasivo foi o mais comum, ocorrendo em 77,11% dos casos. Quanto ao grau histológico, o mais comum foi G1/G2 correspondendo a 64,81% da amostra. Sobre o estágio clínico, o mais frequente foi o estágio II (53,07%). Além disso, as formas de tratamento mais utilizadas foram: mastectomia radical (82,80%); quimioterapia adjuvante (79,47%) e radioterapia (63,47%). Quanto ao SII, a proporção de pacientes com índice baixo e alto foram semelhantes, respectivamente 50,50% e 49,50%.

Risco de Viés nos Estudos Incluídos

O risco de viés dos estudos incluídos pode ser observado na figura 2. Com relação ao percentual de respostas positivas, podemos observar que houve uma variação compreendendo de 88,89 a 100%. É importante destacar que apenas o estudo de Giorgi et al., 2019[18] apresentou uma resposta "não" com relação ao questionamento que se referia ao *follow up*. Porém a porcentagem de respostas positivas de cada estudo foi superior a 70%, caracterizando-os como baixo risco de viés.

Resultados individuais dos estudos

O estudo de Giorgi et al., 2019[18]avaliou a relação entre as células tumorais circulantes e os escores baseados na inflamação de pacientes com câncer de mama metastático, englobando de forma geral os subtipos moleculares. No total foram avaliadas 519 mulheres. Dessas, 124 pacientes possuíam o diagnóstico de TNBC. Desta forma, foi possível investigar o prognóstico através da OS, bem como estimar o HR e seus intervalos de confiança por meio de uma análise univariada. Como *cut off* para o SII, foi adotado o valor de 836, sendo verificado que 65 pacientes apresentaram um baixo índice e 59 altos SII. Vale destacar que neste estudo alto SII não foi considerado preditor de OS [HR = 1,18 (0,71-1,97), p<0,522].

Liu et al., 2019[16] avaliaram a significância do prognóstico do SII associado a OS e DFS em 160 pacientes que receberam o diagnóstico de câncer de mama triplo negativo. Dos 160 pacientes avaliados, 143 e 140 apresentaram recorrência tumoral e metástase à distância, respectivamente, e 119 morreram. O ponto de corte calculado para SII foi de 557. Sendo assim, 80 pacientes apresentaram SII considerado baixo e a outra metade apresentaram SII alto. Desta forma, o estudo revelou que SII prediz OS [HR (análise univariada) = 2,91 (2,0-4,23), p<0,001; HR (análise multivariada) = 2,6 (1,74-3,88), p<0,001]. SII também prediz DFS [HR (análise

univariada) = 1,88 (1,34-2,65), p<0,001; HR (análise multivariada) = 1,46 (1,01-2,12), p<0,045].

Acerca da pesquisa de Wang et al., 2019[17], destaca-se que foi explorado a relação entre o SII e sistemas de relatórios e dados de imagem da mama (BI-RADS) em pacientes com o diagnóstico de câncer de mama triplo negativo. Além disso, também foi avaliado a OS e DFS no grupo de estudo. Após os cálculos para o ponto de corte do SII, estabeleceu o valor de 624, sendo que 108 pacientes foram considerados como tendo SII alto e 107 SII baixo. Desta forma, o estudo mostrou que SII é preditor da OS [HR (análise univariada) = 3,78 (2,16-4,15), p<0,001; HR (análise multivariada) = 2,96 (2,18-3,98), p<0,001] e DFS [HR (análise univariada) = 3,16 (1,82-4,02), p<0,001; HR (análise multivariada) = 2,85 (1,62-3,81), p<0,005].

Síntese dos Resultados

Para síntese dos resultados realizou-se metanálises para OS e DFS, agrupadas por análise univariada e multivariada. Acerca da OS, podemos observar (figura 3) que SII em níveis elevados é fator prognóstico para pior sobrevida [HR (análise univariada) = 2,41 (1,23-4,71), p=0,01); HR (análise multivariada) = 2,82 (2,22-3,59), p<0,01]. Destaca-se que esses dados apresentaram alta heterogeneidade estatística na análise univariada (I^2 = 86%, p<0,01). Em relação à DFS, observa-se (figura 4) que alto SII também é preditor da sobrevida [HR (análise univariada) = 2,41 (1,45-4,01), p<0,01; HR (análise multivariada) = 2,02 (1,05-3,89), p=0,04]. Observou-se aqui alta heterogeneidade estatística, que não pôde ser investigada devido ao número reduzido de estudos que entrou na metanálise.

Certeza da Evidência

A tabela 3 consiste no resumo dos achados para a certeza da evidência. A certeza da evidência foi considerada muito baixa tanto para OS como para DFS. O motivo para tal resultado foi devido a presença de viés de publicação, alta heterogeneidade de ambos desfechos, e amplo intervalo de confiança.

DISCUSSÃO

Na presente revisão sistemática, demostrou-se que SII é um fator prognóstico independente no TNBC. Observamos que as pacientes com diagnóstico de TNBC que apresentaram o SII alto apresentaram menor tempo de OS e DFS.

Vale ressaltar que a grande maioria dessas pacientes se encontravam em estágios iniciais, tendo como tratamento mastectomia radical, quimioterapia adjuvante e radioterapia. Assim como encontrado na literatura, nesse subtipo, as pacientes recebem o diagnóstico nas fases iniciais do câncer, porém é importante destacar que o TNBC é caracterizado por apresentar uma atividade proliferativa intensa, elevada taxa de crescimento, curso clínico agressivo, metástase precoce, e consequentemente prognóstico negativo[19-20].

O SII foi descrito pela primeira vez por Hu et al., 2014[8], que avaliou o SII como preditor no prognóstico do carcinoma hepatocelular e definiu como um indicador promissor que permite avaliar de forma integrada o equilíbrio entre os componentes imunológicos e inflamatórios do hospedeiro podendo, desta forma, predizer o prognóstico e, consequentemente, influenciar nas modalidades de tratamento a serem adotadas. O seu cálculo foi descrito da seguinte maneira: SII= P x N/L, onde P, N e L são plaquetas, neutrófilos e linfócitos, respectivamente. A significância do seu prognóstico para o TNBC começou a ser investigado através do estudo de Liu et al., 2019[16] em que foram avaliadas a relação do valor de SII com as seguintes variáveis: OS, DFS e Sobrevida de Metástase Livre a Distância (DMFS).

A respeito do mecanismo de associação, sabe-se que a quantidade elevada de células inflamatórias circulantes favorece a progressão do processo de carcinogênese[6]. Estudos apontam que as plaquetas atuam protegendo as células tumorais circulantes contra tensões de cisalhamento dentro dos vasos, induzindo a transição epitélio-mesenquimal, favorecendo a migração dessas células para sítios metastáticos. Enquanto os neutrófilos atuam promovendo a adesão e proliferação celular por meio da secreção do Fator de Crescimento Endotelial Vascular (VEGF). E os linfócitos induzirão a morte celular citotóxica, inibindo dessa forma a migração e proliferação de células tumorais, determinado a resposta imunológica do hospedeiro à malignidade[5-7].

Sobre esse parâmetro, Zhang et al., 2020[21] elaboraram uma revisão sistemática e metanálise incluindo 8 estudos, totalizando 2642 pacientes que receberam diagnóstico de câncer de mama. Foram avaliados três tipos de desfechos: OS, DFS e DMFS. O valor prognóstico foi estimado por HR e RR. Os dados obtidos mostraram que os pacientes com SII

em níveis elevados apresentaram pior OS (HR = 1,79 (1,33–2,42), $p < 0,001$), DFS (HR = 1,79 (1,31–2,46), p < 0,001) e DMFS (HR = 1,64 (1,32–2,03), $p < 0,001$). Além disso, o SII alto se associou com a presença de metástase linfonodal e estágio TNM avançado.

Ji et al. 2020[22] também realizaram uma revisão sistemática com metanálise, tendo incluídos 9 estudos (2724 pacientes). Os autores avaliaram o valor de SII como preditor de prognóstico no câncer de mama e câncer ginecológico. O valor de prognóstico foi estimado por HR e RR. Os resultados mostraram que SII alto esteve relacionado com pior OS [HR = 2,12 (1,61–2,79), $p< 0,001$] e pior DFS [HR = 2,28 (1,52–3,41), $p <0,001$), além de um maior risco de metástase linfonodal (RR = 1,34 (1,20–1,50) $p <0,001$). Sendo assim, o presente estudo evidenciou que o SII se mostrou um indicador promissor em cânceres ginecológicos e de mama.

Por conseguinte, a presente revisão sistemática se fez necessária para investigar o papel prognóstico do SII especificadamente no TNBC. Apesar do presente estudo ter mostrado significância estatística desse parâmetro nas metanálises, esses achados foram classificados como tendo evidência muito baixa em virtude da presença de viés de publicação, alta heterogeneidade, e amplo intervalo de confiança dos HR agrupados. O número reduzido de estudos sugeriu o viés de publicação e impediu a investigação da heterogeneidade, podendo ainda ter contribuído para o amplo intervalo de confiança.

Dessa forma, novos estudos primários são necessários e futuras revisões sistemáticas poderão trazer melhores evidências sobre a associação entre SII e sobrevida nessa patologia, e assim poder contribuir para implantação desse índice na avaliação dos pacientes com o diagnóstico de TNBC.

CONCLUSÃO

Na presente revisão sistemática evidenciamos que existe associação entre os níveis de SII com OS e DFS, podendo ser considerado um preditor prognóstico independente em pacientes com o diagnóstico de câncer de mama triplo negativo. Apesar de significativos, os dados apresentados nessa revisão, apresentam certeza da evidência muito baixa devido principalmente ao número reduzido de estudos incluídos. Sendo assim, há necessidade de se realizarem novos estudos primários que investiguem a influência de SII no prognóstico do câncer de mama triplo negativo.

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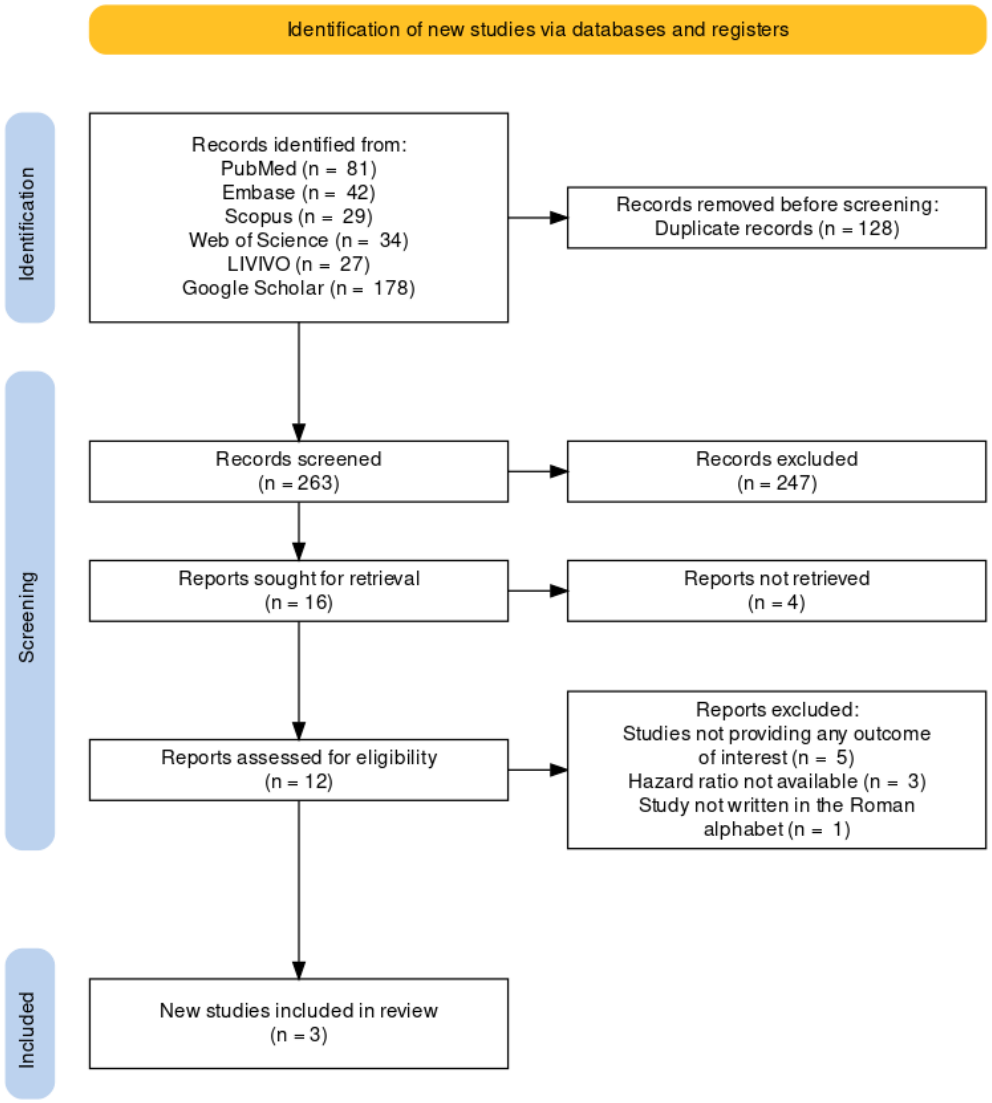
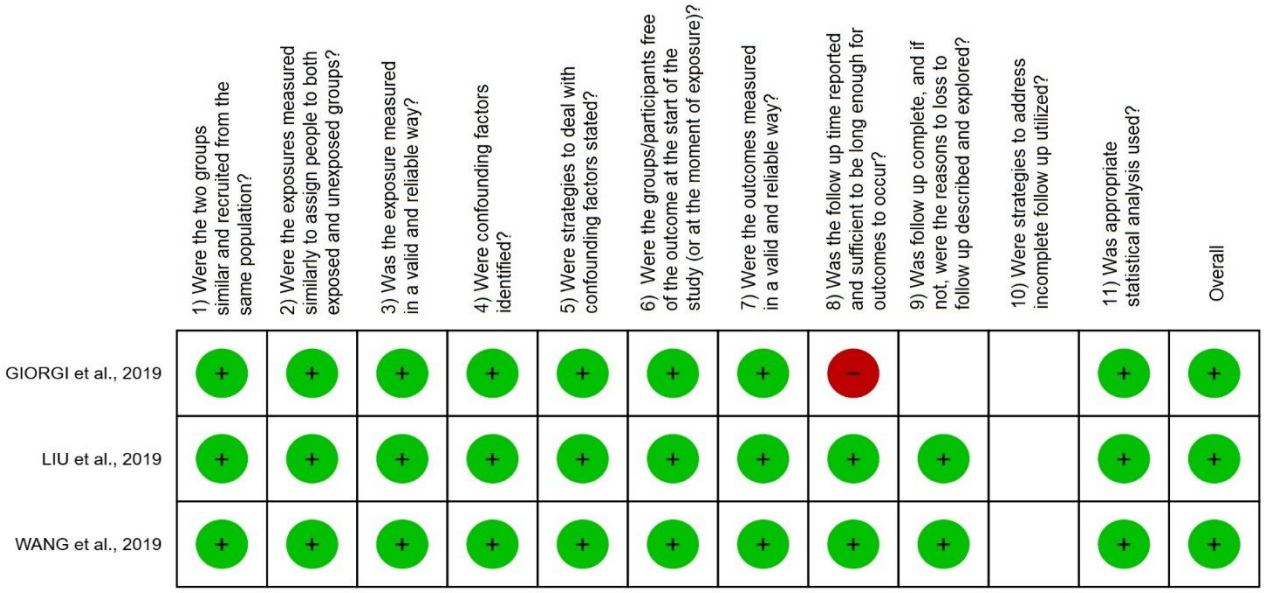
Figura 1: Diagrama de fluxo da pesquisa bibliográfica e seleção dos estudos.



Fonte: Autores.

Fig. 2. Risco de viés dos estudos.



Fonte: Autores

Figura 3 – Meta-análises para sobrevida global. (A) Análise univariada, (B) análise multivariada.

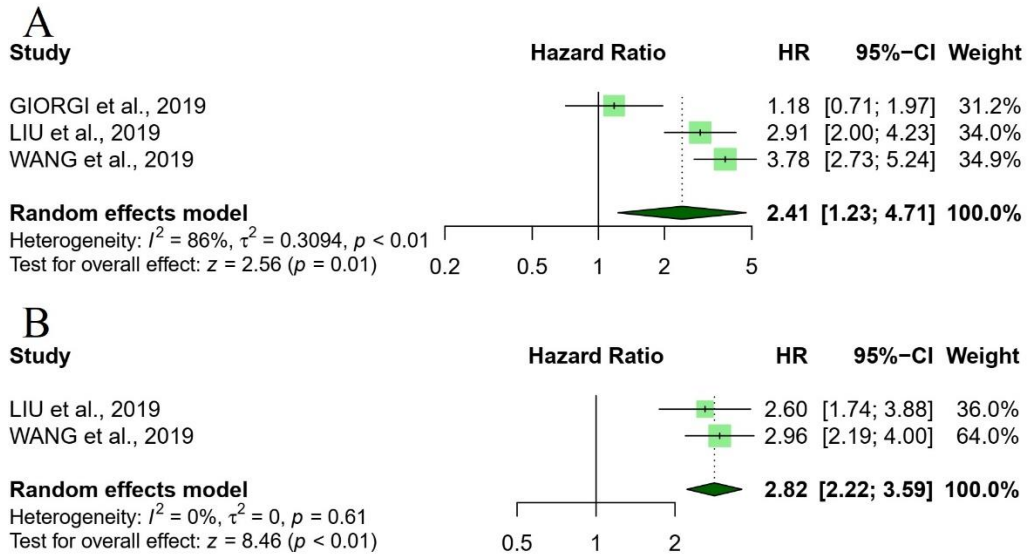


Figura 4 – Meta-análises para sobrevida livre da doença. (A) Análise univariada, (B) análise multivariada.

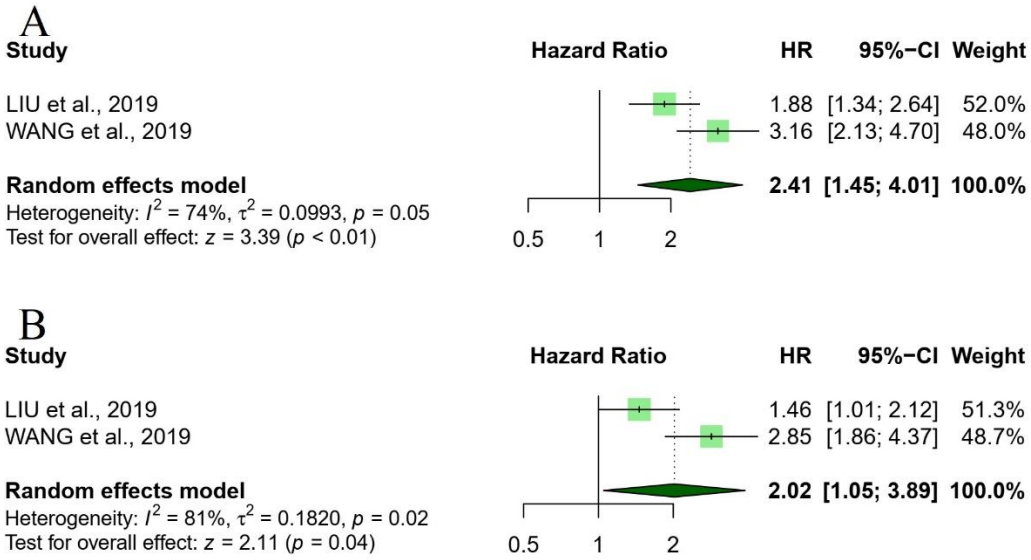


Tabela 1: Resumo das características descritivas dos estudos incluídos

Autor	Ano	País	Tipo de estudo	Amostra	Desfecho
Giorgi *et al*.	2019	EUA	Coorte	124	Sobrevida global: HR (análise univariada) = 1,18 (0,71-1,97), p<0,522.
Liu *et al.*	2019	China	Coorte	160	Sobrevida global: HR (análise univariada) = 2,91 (2,0-4,23), p<0,001; HR (análise multivariada) = 2,6 (1,74-3,88), p<0,001. Sobrevida livre da doença: HR (análise univariada) = 1,88 (1,34-2,65), p<0,001; HR (análise multivariada) = 1,46 (1,01-2,12), p<0,045.
Wang *et al*	2019	China	Coorte	215	Sobrevida global: HR (análise univariada) = 3,78 (2,16-4,15), p<0,001; HR (análise multivariada) = 2,96 (2,18-3,98), p<0,001. Sobrevida livre da doença: HR (análise univariada) = 3,16 (1,82-4,02), p<0,001; HR (análise multivariada) = 2,85 (1,62-3,81), p<0,005.

EUA, Estados Unidos; HR, Hazard Ratio.

Tabela 2: Estimativas agrupadas para características demográficas e clínico-patológicas dos pacientes

Characteristics	Effect size (%)	95% CI	Heterogeneity	
			I^2 (%)	p
Follow-up (months)	61.87*	[42.06; 81.69]	98	< 0.01
Tumor				
pT1	22.07	[17.88; 26.27]	0	0.52
pT2	58.13	[53.14; 63.13]	0	1.00
pT3	16.99	[13.19; 20.79]	0	0.52
pT4	2.66	[1.03; 4.29]	0	0.86
Lymph node				
pN0	42.38	[37.38; 47.38]	0	0.50
pN1	32.53	[27.79; 37.27]	0	0.81
pN2	14.66	[11.08; 18.24]	0	0.89
pN3	10.33	[7.25; 13.41]	0	0.57
Tumor histology				
Invasive ductal carcinoma	77.11	[72.86; 81.36]	0	0.57
Invasive lobular carcinoma	22.89	[18.64; 27.14]	0	0.57
Histologic grade				
G1/G2	64.81	[59.97; 69.64]	0	0.77
G3	34.64	[29.83; 39.46]	0	0.59
Stages				
I	14.86	[11.27; 18.46]	0	0.54
II	53.07	[48.02; 58.12]	0	0.98
III	31.98	[27.26; 36.70]	0	0.62
Surgery				
Breast-conserving surgery	17.20	[13.38; 21.01]	0	0.37
Radical mastectomy	82.80	[78.99; 86.62]	0	0.37
Chemotherapy				
Adjuvant	79.47	[75.39; 83.56]	0	0.82
Neoadjuvant	20.53	[16.44; 24.61]	0	0.82
radiotherapy	63.47	[58.60; 68.35]	0	0.75
SII				
Low	50.50	[46.16; 54.89]	0	0.88
High	49.50	[45.11; 53.88]	0	0.88

*Mean; CI, confidence interval; SII, Systemic Immunoinflammation Index.

Tabela 3 - GRADE summary of findings

Certainty assessment							
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Certainty**
Outcome 1: Overall Survival Univariate analysis (HR = 2.41; 95% CI: 1.23-4.71, p = 0.01); multivariate analysis (HR = 2.82; 95% CI: 2.22-3.59, p<0.01)							
3	observational studies	not serious	very serious[a]	not serious	serious[b]	publication bias strongly suspected[c]	⊕◯◯◯ Very low
Outcome 2: Disease Free Survival Univariate analysis (HR = 2.41; 95% CI: 1.45-4.01, p < 0.01); multivariate analysis (HR = 2.02; 95% CI: 1.05-3.89, p = 0.04)							
2	observational studies	not serious	very serious[a]	not serious	serious[b]	publication bias strongly suspected[c]	⊕◯◯◯ Very low

a, High heterogeneity; b, Wide confidence interval; c, Small number of studies; CI, confidence interval.

Tabela Suplementar 1: Estratégias de busca utilizadas nas diferentes bases de dados.

PubMed
("Breast Neoplasms"[Mesh] OR "Breast Neoplasms" OR "Breast Neoplasm" OR "Breast Tumors" OR "Breast Tumor" OR "Breast Cancer" OR "Mammary Cancer" OR "Mammary Cancers" OR "Malignant Neoplasm of Breast" OR "Breast Malignant Neoplasm" OR "Breast Malignant Neoplasms" OR "Malignant Tumor of Breast" OR "Breast Malignant Tumor" OR "Breast Malignant Tumors" OR "Cancer of Breast" OR "Cancer of the Breast" OR "Human Mammary Carcinomas" OR "Human Mammary Carcinoma" OR "Human Mammary Neoplasm" OR "Human Mammary Neoplasms" OR "Breast Carcinoma" OR "Breast Carcinomas" OR "Triple Negative Breast Neoplasms"[Mesh] OR "Triple Negative Breast Neoplasms" OR "ER-Negative PR-Negative HER2-Negative Breast Neoplasms" OR "ER Negative PR Negative HER2 Negative Breast Neoplasms" OR "Triple-Negative Breast Cancer" OR "Breast Cancer, Triple-Negative" OR "Breast Cancers, Triple-Negative" OR "Triple-Negative Breast Cancers" OR "Triple-Negative Breast Neoplasm" OR "Breast Neoplasm, Triple-Negative" OR "Breast Neoplasms, Triple-Negative" OR "Triple Negative Breast Neoplasm" OR "Triple-Negative Breast Neoplasms" OR "ER-Negative PR-Negative HER2-Negative Breast Cancer" OR "ER Negative PR Negative HER2 Negative Breast Cancer" OR "Triple Negative Breast Cancer") AND ("immune-inflammation index" OR "SII" OR "systemic immune-inflammation index" OR "systemic immune inflammation index" OR "neutrophil×platelets/lymphocyte" OR "systemic-immune-inflammation index" OR "platelet × neutrophil/lymphocyte" OR "platelet count×NLR" OR "systemic immune-inflammatory index") AND ("Prognosis"[Mesh] OR "Prognosis" OR "Prognoses" OR "Prognostic Factors" OR "Prognostic Factor" OR "Survival"[Mesh] OR "Survival" OR "disease-free survival" OR "overall survival" OR "hazard ratio" OR "cancer-specific survival" OR "disease-specific survival" OR "recurrence-free survival")
Embase
#1 ('breast neoplasms'/exp OR 'breast neoplasms' OR 'breast neoplasm'/exp OR 'breast neoplasm' OR 'breast tumors'/exp OR 'breast tumors' OR 'breast tumor'/exp OR 'breast tumor' OR 'breast cancer'/exp OR 'breast cancer' OR 'mammary cancer'/exp OR 'mammary cancer' OR 'mammary cancers' OR 'malignant neoplasm of breast' OR 'breast malignant neoplasm' OR 'breast malignant neoplasms' OR 'malignant tumor of breast' OR 'breast malignant tumor' OR 'breast malignant tumors' OR 'cancer of breast' OR 'cancer of the breast'/exp OR 'cancer of the breast' OR 'human mammary

carcinomas' OR 'human mammary carcinoma'/exp OR 'human mammary carcinoma' OR 'human mammary neoplasm' OR 'human mammary neoplasms' OR 'breast carcinoma'/exp OR 'breast carcinoma' OR 'breast carcinomas' OR 'triple negative breast neoplasms'/exp OR 'triple negative breast neoplasms' OR 'er-negative pr-negative her2-negative breast neoplasms' OR 'er negative pr negative her2 negative breast neoplasms' OR 'triple-negative breast cancer'/exp OR 'triple-negative breast cancer' OR 'breast cancer, triple-negative' OR 'breast cancers, triple-negative' OR 'triple-negative breast cancers'/exp OR 'triple-negative breast cancers' OR 'triple-negative breast neoplasm'/exp OR 'triple-negative breast neoplasm' OR 'breast neoplasm, triple-negative' OR 'breast neoplasms, triple-negative' OR 'triple negative breast neoplasm'/exp OR 'triple negative breast neoplasm' OR 'triple-negative breast neoplasms'/exp OR 'triple-negative breast neoplasms' OR 'er-negative pr-negative her2-negative breast cancer' OR 'er negative pr negative her2 negative breast cancer' OR 'triple negative breast cancer'/exp OR 'triple negative breast cancer')

#2 ('immune-inflammation index' OR 'sii' OR 'systemic immune-inflammation index' OR 'systemic immune inflammation index'/exp OR 'systemic immune inflammation index' OR 'neutrophil×platelets/lymphocyte' OR 'systemic-immune-inflammation index' OR 'platelet × neutrophil/lymphocyte' OR 'platelet count×nlr' OR 'systemic immune-inflammatory index')

#3 ('prognosis'/exp OR 'prognosis' OR 'prognoses' OR 'prognostic factors' OR 'prognostic factor'/exp OR 'prognostic factor' OR 'survival'/exp OR 'survival' OR 'disease-free survival'/exp OR 'disease-free survival' OR 'overall survival'/exp OR 'overall survival' OR 'hazard ratio'/exp OR 'hazard ratio' OR 'cancer-specific survival'/exp OR 'cancer-specific survival' OR 'disease-specific survival'/exp OR 'disease-specific survival' OR 'recurrence-free survival'/exp OR 'recurrence-free survival')

#1 AND #2 AND #3

Web of Science

((ALL=("Breast Neoplasms" OR "Breast Neoplasm" OR "Breast Tumors" OR "Breast Tumor" OR "Breast Cancer" OR "Mammary Cancer" OR "Mammary Cancers" OR "Malignant Neoplasm of Breast" OR "Breast Malignant Neoplasm" OR "Breast Malignant Neoplasms" OR "Malignant Tumor of Breast" OR "Breast Malignant Tumor" OR "Breast Malignant Tumors" OR "Cancer of Breast" OR "Cancer of the Breast" OR "Human Mammary Carcinomas" OR "Human Mammary Carcinoma" OR "Human Mammary Neoplasm" OR "Human Mammary Neoplasms" OR "Breast Carcinoma" OR "Breast Carcinomas" OR "Triple Negative Breast Neoplasms" OR "ER-Negative PR-Negative HER2-Negative Breast Neoplasms" OR "ER Negative PR Negative HER2 Negative Breast Neoplasms" OR "Triple-Negative Breast Cancer" OR "Breast Cancer, Triple-Negative" OR "Breast Cancers, Triple-Negative" OR "Triple-Negative Breast Cancers" OR "Triple-Negative Breast Neoplasm" OR "Breast Neoplasm, Triple-Negative" OR "Breast Neoplasms, Triple-Negative" OR "Triple Negative Breast Neoplasm" OR "Triple-Negative Breast Neoplasms" OR "ER-Negative PR-Negative HER2-Negative Breast Cancer" OR "ER Negative PR Negative HER2 Negative Breast Cancer" OR "Triple Negative Breast Cancer")) AND ALL=("immune-inflammation index" OR "SII" OR "systemic immune-inflammation

index" OR "systemic immune inflammation index" OR "neutrophil×platelets/lymphocyte" OR "systemic-immune-inflammation index" OR "platelet × neutrophil/lymphocyte" OR "platelet count×NLR" OR "systemic immune-inflammatory index")) AND ALL=("Prognosis" OR "Prognoses" OR "Prognostic Factors" OR "Prognostic Factor" OR "Survival" OR "disease-free survival" OR "overall survival" OR "hazard ratio" OR "cancer-specific survival" OR "disease-specific survival" OR "recurrence-free survival")
Scopus
TITLE-ABS-KEY("Breast Neoplasms" OR "Breast Neoplasm" OR "Breast Tumors" OR "Breast Tumor" OR "Breast Cancer" OR "Mammary Cancer" OR "Mammary Cancers" OR "Malignant Neoplasm of Breast" OR "Breast Malignant Neoplasm" OR "Breast Malignant Neoplasms" OR "Malignant Tumor of Breast" OR "Breast Malignant Tumor" OR "Breast Malignant Tumors" OR "Cancer of Breast" OR "Cancer of the Breast" OR "Human Mammary Carcinomas" OR "Human Mammary Carcinoma" OR "Human Mammary Neoplasm" OR "Human Mammary Neoplasms" OR "Breast Carcinoma" OR "Breast Carcinomas" OR "Triple Negative Breast Neoplasms" OR "ER-Negative PR-Negative HER2-Negative Breast Neoplasms" OR "ER Negative PR Negative HER2 Negative Breast Neoplasms" OR "Triple-Negative Breast Cancer" OR "Breast Cancer, Triple-Negative" OR "Breast Cancers, Triple-Negative" OR "Triple-Negative Breast Cancers" OR "Triple-Negative Breast Neoplasm" OR "Breast Neoplasm, Triple-Negative" OR "Breast Neoplasms, Triple-Negative" OR "Triple Negative Breast Neoplasm" OR "Triple-Negative Breast Neoplasms" OR "ER-Negative PR-Negative HER2-Negative Breast Cancer" OR "ER Negative PR Negative HER2 Negative Breast Cancer" OR "Triple Negative Breast Cancer") AND TITLE-ABS-KEY("immune-inflammation index" OR "SII" OR "systemic immune-inflammation index" OR "systemic immune inflammation index" OR "neutrophil×platelets/lymphocyte" OR "systemic-immune-inflammation index" OR "platelet × neutrophil/lymphocyte" OR "platelet count×NLR" OR "systemic immune-inflammatory index") AND TITLE-ABS-KEY("Prognosis" OR "Prognoses" OR "Prognostic Factors" OR "Prognostic Factor" OR "Survival" OR "disease-free survival" OR "overall survival" OR "hazard ratio" OR "cancer-specific survival" OR "disease-specific survival" OR "recurrence-free survival")
Livivo
("Breast Neoplasms" OR "Breast Neoplasm" OR "Breast Tumors" OR "Breast Tumor" OR "Breast Cancer" OR "Mammary Cancer" OR "Mammary Cancers" OR "Malignant Neoplasm of Breast" OR "Breast Malignant Neoplasm" OR "Breast Malignant Neoplasms" OR "Malignant Tumor of Breast" OR "Breast Malignant

Tumor" OR "Breast Malignant Tumors" OR "Cancer of Breast" OR "Cancer of the Breast" OR "Human Mammary Carcinomas" OR "Human Mammary Carcinoma" OR "Human Mammary Neoplasm" OR "Human Mammary Neoplasms" OR "Breast Carcinoma" OR "Breast Carcinomas" OR "Triple Negative Breast Neoplasms" OR "ER-Negative PR-Negative HER2-Negative Breast Neoplasms" OR "ER Negative PR Negative HER2 Negative Breast Neoplasms" OR "Triple-Negative Breast Cancer" OR "Breast Cancer, Triple-Negative" OR "Breast Cancers, Triple-Negative" OR "Triple-Negative Breast Cancers" OR "Triple-Negative Breast Neoplasm" OR "Breast Neoplasm, Triple-Negative" OR "Breast Neoplasms, Triple-Negative" OR "Triple Negative Breast Neoplasm" OR "Triple-Negative Breast Neoplasms" OR "ER-Negative PR-Negative HER2-Negative Breast Cancer" OR "ER Negative PR Negative HER2 Negative Breast Cancer" OR "Triple Negative Breast Cancer") AND ("immune-inflammation index" OR "SII" OR "systemic immune-inflammation index" OR "systemic immune inflammation index" OR "neutrophil×platelets/lymphocyte" OR "systemic-immune-inflammation index" OR "platelet × neutrophil/lymphocyte" OR "platelet count×NLR" OR "systemic immune-inflammatory index") AND ("Prognosis" OR "Prognoses" OR "Prognostic Factors" OR "Prognostic Factor" OR "Survival" OR "disease-free survival" OR "overall survival" OR "hazard ratio" OR "cancer-specific survival" OR "disease-specific survival" OR "recurrence-free survival")
Google Scholar
("Triple Negative Breast Cancer" OR "Triple-Negative Breast Cancer") AND ("disease-free survival" OR "overall survival" OR "disease-specific survival") AND ("immune-inflammation index" OR "immune-inflammatory index")

Fonte: Autores.

4 CONCLUSÃO GERAL

Na presente dissertação, por meio de uma revisão sistemática com metanálise, observou-se que SII alto esteve relacionado com baixa OS e DFS no câncer de mama triplo negativo. Desta forma, sugere-se que o SII pode ser considerado um marcador independente no prognóstico do câncer de mama triplo negativo.

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ANEXO: REGIMENTO INTERNO

CAPÍTULO V

DA DEFESA E DO PRODUTO FINAL

Art. 43 Para o processo de defesa do produto final, o discente deverá entregar formulário
assinado por seu orientador ao colegiado do PPGCS, contendo a data, o local, o título do trabalho, resumo do trabalho e o nome componentes da banca examinadora. Ademais, deve entregar o
comprovante de submissão do artigo científico em revista científica com Qualis CAPES mínimoB1 na área da Medicina II e ata de aprovação no exame de qualificação.Para a defesa de dissertação, os pós-graduandos devem ter concluído todos os créditos. O estudante deverá entregar diretamente aos membros da banca as cópias impressas dos trabalhos, respeitando o prazo entre 30 e 15 dias antes da defesa de dissertação.

Clinical Breast Cancer

SYSTEMIC IMMUNE-INFLAMMATION INDEX AS A FACTOR FOR THE PROGNOSIS OF TRIPLE NEGATIVE BREAST CANCER: SYSTEMATIC REVIEW WITH META-ANALYSIS

--Manuscript Draft--

Manuscript Number:	
Article Type:	Systematic Review or Meta-analysis
Keywords:	Triple Negative; Breast Neoplasms; prognosis; Systemic Immune-Inflammation Index
Corresponding Author:	Filipe Nobre Chaves Universidade Federal do Ceará - Campus Sobral Sobral, CE BRAZIL
First Author:	Camila Melo Mesquita
Order of Authors:	Camila Melo Mesquita
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Abstract:	The Systemic Immuno-Inflammation Index is used as an independent prognostic factor for some types of cancer, however there are still few studies that correlate the SII value with the prognosis of triple negative breast cancer. Therefore, the present study sought to identify, through a meta-analysis, clinicopathological aspects and the prognostic value of Systematic Immune-Inflammation in patients with triple negative breast cancer. Thus, we performed a bibliographical research in the following databases: PubMed, Embase, Scopus and Web of Science, Livivo and Google Scholar. As inclusion criteria, we considered articles that were published until the year of 2023, there were no restrictions regarding the language of publication, primary studies that addressed the relationship between Systemic Immune-Inflammation Index and the prognosis of patients with triple negative breast cancer, with the outcomes being Overall Survival and Disease Free Survival. Literature reviews, series and case reports, duplicate studies, animal studies and studies with insufficient data were excluded. The prognostic value was estimated using Hazard Ratio (HR) and Relative Risk with a Confidence Interval of 95%. The results of the multivariate meta-analysis showed that high SII is a prognostic factor for Overall Survival and Disease Free Survival: [HR (univariate analysis) = 2.41 (1.23-4.71), p=0.01); HR (multivariate analysis) = 2.82 (2.22-3.59), p<0.01] and [HR (univariate analysis) = 2.41 (1.45-4.01), p<0, 01; HR (multivariate analysis) = 2.02 (1.05-3.89), p=0.04], respectively. Although our study shows that IBS is a promising indicator for prognosis in TNBC, there is still a need for further studies on the subject.
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[dataset] 6. Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. https://doi.org/10.17632/xwj98nb39r.1
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7. Coon E, Berndt M, Jan A, Svyatsky D, Atchley A, Kikinzon E, Harp D, Manzini G, Shelef

E, Lipnikov K, Garimella R, Xu C, Moulton D, Karra S, Painter S, Jafarov E, Molins S. Advanced Terrestrial Simulator (ATS) v0.88 (Version 0.88). Zenodo; 2020, March 25. https://doi.org/10.5281/zenodo.3727209

Prescription information: Taxol (paclitaxel) Injection [prescribing information]: Princeton, NJ: Bristol-Myers Squibb; 2003.

Erratum: Loehrer PJ, Sr., Einhorn LH, Elson PJ, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study [published erratum appears in: J Clin Oncol 1993;11:384]. J Clin Oncol 1992; 10:1066-73.

Non-English Language Translations: Zhang N, Gong K, Yang XY, et al. Expression of hypoxia-inducible factor-1-alpha, hypoxia-inducible factor-2alpha and vascular endothelial growth factor in sporadic clear cell renal cell renal cell carcinoma and their significance in the pathogenesis thereof. [in Chinese]. Zhonghua Yi Xue Za Zhi 2006; 86:1526-9.

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