Rev. Cuerpo Med. HNAAA, Vol 17(1) - 2024

REVISTA DEL CUERPO MÉDICO HOSPITAL NACIONAL ALMANZOR AGUINAGA ASENJO, CHICLAYO, PERÚ

ISSN | impresa: 2225-5109; Electrónica: 2227-4731

Cross Ref. DOI: 10.35434/rcmhnaaa | OJS https://cmhnaaa.org.pe/ojs

Original Article

Neutrophil-to-lymphocyte ratio and survival outcomes in testicular cancer: A systematic review and meta-analysis

Índice Neutrófilo-Linfocito y desenlaces de supervivencia en cáncer testicular : Revisión sistemática y meta análisis

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DOI

https://doi.org/10.35434/rcmhnaaa.2024.171.2048

ABSTRACT

Background: The neutrophil-to-lymphocyte ratio (NLR) is a biomarker in inflammatory processes associated with multiple unfavorable outcomes in various diseases. This study aims to evaluate the association between NLR values and survival outcomes in patients diagnosed with testicular cancer.
Methods: A systematic search was conducted in 6 electronic databases to retrieve studies evaluating NLR in patients with testicular cancer. The outcomes sought were overall survival (OS) and progression-free survival (PFS), and the effect measures were hazard ratio (HR) with a 95% confidence interval (CI). A random effects model was used for the meta-analysis. The risk of bias included in the studies was assessed according to the Newcastle-Ottawa Scale criteria. Egger test and Trim-and-fill method were used to test the publication bias among articles. **Results:** Six cohort studies (n= 1315) were evaluated. High NLR values are associated with a higher risk of OS (HR: 1.75; 95% CI 1.04 - 2.92, I2: 65%). However, no statistically significant association was found between NLR and PFS values. We found publication bias in the association between NLR and OS (Egger test < 0.1). This bias was corrected by using the trim-and-fill method (HR: 1.38, 95% CI 0.85 - 2.22). **Conclusions:** High NLR values are associated with worse OS; however, this result had publication bias, and the association was lost when this bias was corrected. Furthermore, no statistically significant association was found between NLR values and PFS.xxxx.

Keywords: Testicular Cancer; neutrophil-lymphocyte ratio; survival; meta-analysis (Source: MeSH-NLM).

RESUMEN

Introducción: El cáncer testicular es la neoplasia maligna sólida más común en pacientes jóvenes entre 15 y 44 años , con tendencia al alza durante la última década. **Objetivo :** Evaluar los valores del índice Neutrófilo-Linfocito (INL) en la supervivencia de pacientes diagnosticados con cáncer testicular. Materiales y **Métodos:** Metanálisis de modelo de efectos aleatorios evaluando la supervivencia general y la supervivencia libre de progresión , cumpliendo 6 estudios con los criterios de inclusión. **Resultados:** Se incluyeron 6 estudios , de los cuales se obtuvo una población total de 1315 . Se evaluó los niveles altos del INL , los cuales se asociaron a una menor supervivencia general (HR: 1.75;IC del 95%: 1,04 - 2,92, I2 : 65%). **Conclusión:** Se encontró asociación entre niveles elevados de INL y menor supervivencia general , a pesar de esto se determinó que este resultado presenta sesgo de publicación , presentando falta de asociación en este resultado.

Palabras Clave: Cáncer testicular; Indice Neutrófilo-Linfocito (INL) , Supervivencia general , Supervivencia libre de progresión (Fuente: DeCS-BIREME).

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CONFLICTS OF INTEREST
authors declared no conflict of interest.

FINANCING
None.

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Conceptualization, A.C-A and D.C-P; Data curation, A.C-A, D.C-P, J.R.U-B and E.A.H-B ; Formal analysis, A.C-A, D.C-P and E.A.A-B; Methodology, A.C-A, D.C-P, J.R.U-B, , E.A.H-B, E.A.A-B and M.D.M-R; Writing-original draft, A.C-A, D.C-P and M.D.M-R.; Writing-review & editing, A.C-A, D.C-P, P.H.-A and V.A.B.-Z. All authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGMENTS
None.

PEER REVIEW
Received: 09/06/2023
Accepted: 12/03/2024

Printer Version: ISSN: 2225-5109
Electronic Version: ISSN: 2227-4731
Cross Ref. DOI: 10.35434/rcmhnaaa
OJS: https://cmhnaaa.org.pe/ojs

HOW TO CITE
Campos-Aspajo A, Caman-Peña D, Ulloque-Badaracco JR, Hernandez-Bustamante EA, Alarcón-Braga EA, Mosquera-Rojas MD, Herrera-Añazco P, Benites-Zapata VA. Índice Neutrófilo-Linfocito y desenlaces de supervivencia en cáncer testicular : Revisión sistemática y meta analisis . Rev. Cuerpo Med. HNAAA [Internet]. 13 de abril de 2024 [citado 26 de marzo de 2025];17(1). DOI: 10.35434/rcmhnaaa.2024.171.2048.

INTRODUCTION

Testicular cancer is the most common solid malignancy in young patients between 15 and 44 years[1, 2]. Globally, there was an overall increasing incidence trend of testicular cancer for the past decade, particularly in younger males; the mortality trends of testicular cancer were relatively stable[3]. Regarding the histological classification of this neoplasia type, 95% of these cancers come from germ cells divided into seminomas and nonseminomas. The rest of the cancer are generally tumors of the gonadal stroma (Leydig cells, Sertoli cells, or granulosa cells)[4].

By 2021, the American Cancer Society estimates that there will be 440 deaths from this type of cancer in the United States. This same year, 9,470 new cases of testicular cancer were diagnosed[5]. Despite being a frequent malignant neoplasm in men, it has a high 5-year survival rate, greater than 98% in patients younger than 50 years[6]. This high survival rate is due to three different types of treatment: surgery, chemotherapy, and radiotherapy. Chemotherapy with cisplatin is the foremost option for treating testicular cancer[7].

At least 25% of cancers have chronic inflammation on a pathophysiological basis[8]. Inflammatory processes caused by both infectious processes and autoimmune diseases have been shown to induce various pro-oncogenic mutations, genomic instability, and the development of angiogenesis rather than tumor growth at the cellular level[9,10]. One way to evaluate systemic inflammation development is by assessing the neutrophil-to-lymphocyte ratio (NLR). This biomarker has been considered in high values as an indicator of poor prognosis in various diseases[11, 12], including urological cancers; however, although there are studies that have evaluated its prognostic value in patients with testicular cancer, to the best of our knowledge, the available evidence has not been systematized[1, 13]. Therefore, the present study aims to evaluate the prognostic value of NLR in testicular cancer.

METHODS

Research question and study design

The research question for this systematic review was based on PECO strategy: Do patients with testicular cancer (P) and high NLR values (E) have worse survival outcomes(O) than similar patients with normal NLR values (C)? Our primary outcome was Overall Survival (OS). Progression-free survival (PFS) was considered a secondary outcome (See definitions of the outcomes for each study in Supplementary Table S1).

Register and report guidelines

We uploaded a summarized protocol version of this systematic review to the International Prospective Register of Systematic Reviews (PROSPERO) with code CRD42021268896. The report was drafted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[14].

Search strategy and databases

We follow the Peer Review of Electronic Search Strategies (PRESS) Guidelines[15] for building the search strategy, which is attached as supplemental material (see Search Strategy in Appendix 1). On March 25, 2022, we systematically searched databases (PubMed, Web of Science, Ovid/Medline, Scielo, Scopus, and LILACS) with no language or date restriction. A manual search was conducted in preprints repositories (Research Square, MedRxiv, Scielo Preprints). The search formula was built using MeSH terms for “testicular cancer” and free terms for “neutrophil to lymphocyte ratio”. Afterwards, this was adapted to other databases.

Eligibility criteria and study selection

The systematic search was focused on retrieving studies assessing NLR prognostic value on testicular cancer. Inclusion criteria were studies with case-control or cohort designs (i), conducted in adult patients (>15) diagnosed with testicular neoplasm (ii), that report NLR values on these patients (iii), and with OS or PFS as outcomes (iv). Research letters and conferences were excluded.

All retrieved records from the systematic search were exported to Rayyan[16] to remove duplicates and select references. According to inclusion criteria, four authors (AC-A, DC-P, EAA-B, EAH-B) independently screened search results by titles and abstracts. The remaining references were reviewed in full text, and the same four authors included studies with all eligibility criteria. Conflicts or discrepancies were resolved by consensus.

Data extraction and statistical analysis

Four authors independently conducted the data extraction process (AC-A, DC-P, EAH-B, JRU-B). A data extraction sheet built on Microsoft Excel 2016 collected relevant information from all included studies. Extracted data from each study were study title, first author, publication date, study location, study design, sample size, participants' baseline characteristics (sex, age), cancer type, outcome type (OS or PFS), and Hazard Ratio (HR) with their 95% Confidence Intervals (CI) as association measure between NLR and OS or PFS.

Estimated HR and 95% CI were pooled in a random-effects model meta-analysis using Review Manager 5.4 (RevMan 5.4) (The Cochrane Collaboration, Copenhagen, Denmark). Cochran's Q static and Higgins I2 were conducted to assess heterogeneity. Severe heterogeneity was defined as $p<0.1$ or $I2>60\%$, respectively. A sensitivity analysis, including only high-quality studies, was performed due to severe heterogeneity.

Quality assessment and publication bias

Four authors (AC-A, DC-P, EAA-B, JRU-B) carried out independently a quality assessment of all included studies using the Newcastle-Ottawa Scale (NOS)[17]. High-quality

studies (low risk of bias) were defined as those with at least six stars in the overall score. Publication bias was assessed through the Egger test and the trim-and-fill method using STATA software version 16.0.

RESULTS

Search results

The initial electronic search yielded 88 articles; 54 were removed for being duplicates. Next, we screened the Title/Abstract of 34 articles; of these, only 17 complied with the totality of the selection criteria. After the full-text review, six studies were included in this systematic review (18-23). For further details on the study selection process, see Figure 1.

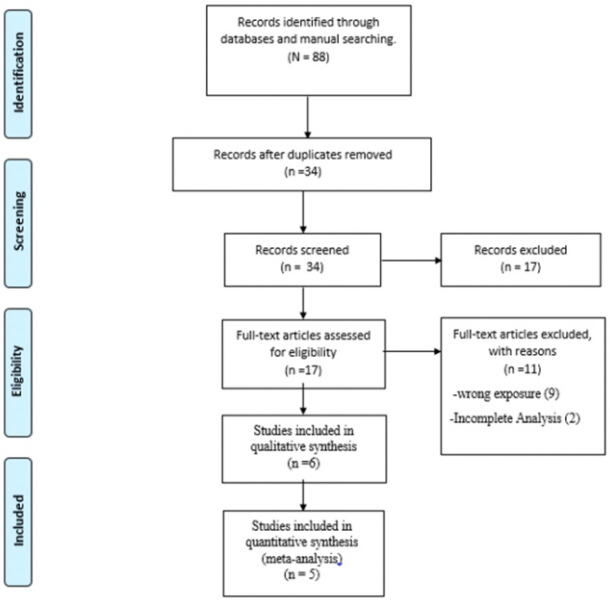

Figure 1. PRISMA Flow Diagram

Study Characteristics

The characteristics of the studies are presented in Table 1. The six articles included cohorts whose populations totaled 1315 participants. The geographical distribution of said articles was as follows: (1) Switzerland, (1) Turkey, (1) Spain, (1) China, (1) Canada, and (1) Japan. The outcome OS was assessed in the six studies, while the outcome PFS was only evaluated in four studies, and the median follow-up time ranged from 23.55 to 63.4 months. The optimal cut-off values for OS ranged from 2.66 to 4.5 and PFS from 2 to 4.1.

The Newcastle-Ottawa Scale was used to assess the quality of the included studies. (See Supplementary Table S2). Five articles were considered low risk of bias, and the remaining study was classified as having a high risk of bias.

OS and NLR

A total of six articles assessed the association between NLR values and OS (n=1315). However, only five studies were included in the meta-analysis because the study of Frankhauser DC et al. reported their NLR values after a log10 transformation (HR: 73.1, 95%CI 3.70 - 1442); including this article in the quantitative synthesis would have introduced bias in the results.

The pooled analysis showed an association between high NLR values and worse OS (HR: 1.75; 95% CI 1.04 - 2.92, I2= 65%) (Figure 2A). In sensitivity analysis, heterogeneity decreased, and the association remained (HR: 2.28, 95% CI 1.28 - 4.05, I2 = 13%) (Figure 2B).

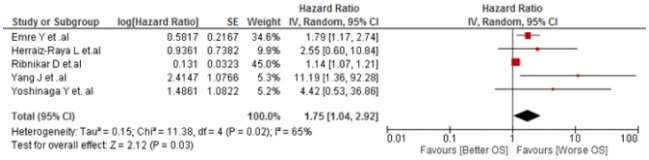

Figure 2A. Association of NLR and OS in patients with testicular cancer

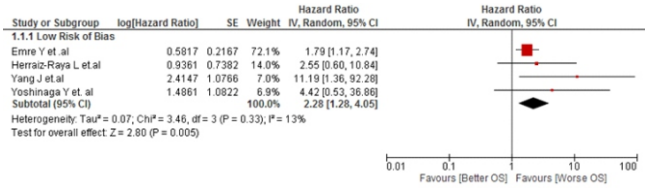

Figure 2B. Sensitivity analysis according to the quality of the studies of the association between NLR and OS in patients with testicular cancer.

PFS and NLR

Four articles assessed the association between NLR values and PFS (n=945). The pooled analysis showed that values of NLR were not statistically significantly associated with PFS (HR: 2.16, 95% CI 0.93 - 5.02, I2= 74%) (Figure 3A). However, in sensitivity analysis, heterogeneity decreased, and the association between higher NLR values and worse PFS became statistically significant (HR: 3.11, 95% CI 1.40 - 6.92, I2 =27%) (Figure 3B).

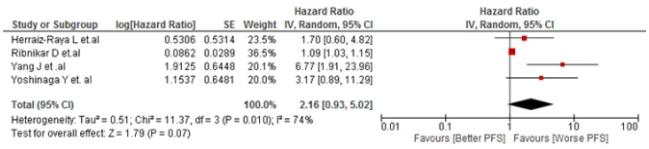

Figure 3A. Association of NLR and PFS in patients with testicular cancer

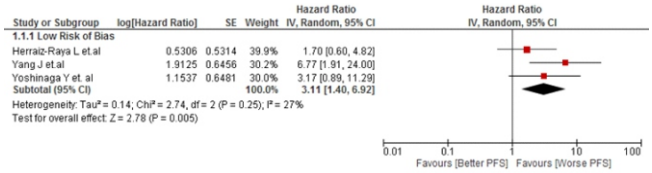

Figure 3B. Sensitivity analysis according to the quality of the studies of the association between NLR and PFS in patients with testicular cancer.

Publication Bias

We found publication bias in the association between NLR and OS (Egger test < 0.1). This bias was corrected by using the trim-and-fill method (HR: 1.38, 95% CI 0.85 to 2.22) (Supplementary Figure S1).

Table 1. Characteristics of included studies

Author	Country	Year	Participants	Median/mean Age (IQR/SD)	Type of testicular cancer	Median follow-up time (months)	Outcome	HR(95% CI)	Cut-off
Fankhauser CD et.al	Switzerland	2018	146	34 (9)	Metastatic Testicular Cancer	53	Overall Survival	73.1(3.70-14.42) A	4.5
Emre Y et.al	Turkey	2021	224	37.72(10)	Non-seminomatous germ-cell tumors and Seminoma	55	Overall Survival	1.789 (1.17-2.735)	NR
Yoshinaga Y et.al	Japan	2021	63	35 (16-67)	Germ cell tumor	63.4	Overall Survival	4.42 (0.53-36.86)	4.1
							Progression free survival	3.17 (0.89-11.26)	
Herraiz-Raya L et.al	Spain	2019	164	31 (30-33)	Germ cell tumor	54	Overall Survival	2.55 (0.6-10.8)	4
							Progression free survival	1.7(0.6- 4.8)	
Yang J et.al	China	2019	28	65 (37-84)	Diffuse Large B-Cell Lymphoma	39.2	Overall Survival	11.186 (1.356-92.276)	2.66
							Progression free survival	6.77 (1.91-23.99)	2.49
Ribnikar D et.al	Canada	2020	690	31 (16-85)	Metastatic Testicular Cancer	23.55	Overall Survival	1.14 (1.07-1.21)	3
							Progression free survival	1.09 (1.03-1.16)	2

NR, Not Reported; 95% CI, 95% Confidence Interval; IQR, Interquartile range; SD, Standard Deviation; A, NLR values after log10 transformation, the HR thus corresponds to a 10-fold increase of the variable.

DISCUSSION

Our main results show that a high NLR value was associated with OS but not with PFS in patients with testicular cancer. However, publication bias was found in the results of the primary outcome, which was corrected with the trim-and-fill method, where there was a loss of the association; due to this, our results should be interpreted with caution.

Although all the pathways involved are not fully understood, inflammation is one of the most prominent elements in the genesis and progression of cancer. In the genesis, inflammation is known as creating reactive oxygen species and activating cell signaling pathways that promote cell proliferation and limit the degree of apoptosis[24, 25]. In progression, its role is known through its effect on the cellular components of the immune system, one of the mediators of inflammation[26]. Additionally, evidence suggests that inflammation, as a chronic state of immune stimulation, is associated with a poor prognosis[27]. In this sense, various inflammation-associated markers have been studied as prognostic markers in different types of cancer[28-30].

As in the rest of urological cancers, in patients with testicular cancer, inflammation seems to play a role in both the genesis and progression of the disease, although the mechanisms are not fully understood. For example, one study found that, although markers of inflammation such as C-reactive protein, albumin, and haptoglobin did not appear to be risk markers for penile cancer, high levels of albumin were predictive of testicular cancer[31]. On the other hand, some studies have shown that C-reactive protein levels predict survival in patients with urological cancers, and the incorporation of CRP in prognostic models for urological cancers improves their predictive accuracy[32]. Along the same lines, various studies have shown the prognostic value of other inflammatory markers, such as the platelet-to-lymphocyte ratio or the lymphocyte-to-monocyte ratio, in patients with testicular cancer[33,34].

The NLR indicates the general immune response to various stress stimuli[11]. In this sense, the NLR is a potential prognostic biomarker in cancers and is of clinical interest due to its accessibility and the ease of calculating this ratio from a routine blood count[35]. Due to its relationship with inflammation, this marker has shown promise in predicting

acute appendicitis[36], severity and mortality in patients with COVID-19[37], relapse in patients with schizophrenia[38], predicting the appearance of rheumatoid arthritis[39], the prognosis of patients with stroke[40] and eye disease[41] or to predict preterm birth[42]. In cancer patients, an overview of systematic reviews and meta-analyses of observational studies found that NLR shows strong evidence for predicting outcomes in composite cancers, cancers treated with immunotherapy, and some specific cancers such as urologic, nasopharyngeal, gastric, and breast cancers, endometrial, soft tissue, sarcoma, and hepatocellular cancers[11]. Although the reasons why NLR is associated with a poor prognosis in cancer patients is associated with its role as an inflammatory marker[11, 13], specifically in patients with testicular cancer, they are not entirely clear. However, part of the explanation may be related to the increased count of neutrophils and lymphocytes in severely ill patients. One study found that testicular cancer patients with elevated NLR values had higher percentages of residual disease and stage II-III tumors[21]. In this sense, the positive association with OS and negative with PFS may be related to the severity of the patients included in the studies, as suggested by research that shows that, in patients with testicular cancer, a high value of NLR is associated with lymph node involvement and metastasis and its predictive value is not independent of risk classification[1].

Our results show sufficient evidence to recommend a high NLR value as a prognostic marker of OS in patients with testicular cancer. We found systematic reviews and meta-analyses of observational studies that found value in the prognostic value of NLR in cancers, including urological cancers[11]. To the best of our knowledge, this study is the first systematic review and meta-analysis that evaluates this association in patients with testicular cancer. Additionally, we performed sensitivity analyses considering the biases of the included studies, which gives robustness to our results.

Our findings suggest a potential low-cost prognostic marker in patients with testicular cancer that will allow healthcare providers to prioritize or individualize management strategies in patients with high NLR values. However, although a sensitivity analysis was performed to limit the heterogeneity of the studies, it is still necessary to consider the characteristics of the patients to interpret the results. In that sense, it is required to consider, for example, scenarios such as whether the patient is post-orchiectomies or received prior chemotherapy[1, 22]. Finally, although this prognostic marker is promising, we cannot affirm that it is superior to other inflammatory markers also evaluated in patients with testicular cancer[33]. Likewise, although the relationship with inflammation is one of the possible explanations for the association found, the exact mechanism that explains our findings is unclear. However, if it is the case that inflammation is the main explanation, it is possible that in concomitant pro-inflammatory states, the predictive value of NFL is limited, as is the case with other markers of inflammation[43]. In that sense, interpretation in these states must be careful.

Limitations

This study has many limitations that should be considered for future research. First, due to the small number of included studies, we could not perform any subgroup analysis according to the sociodemographic and clinical characteristics of the patients. This small number of included studies also did not allow the collection of precise patient selection data, such as the presence of comorbidities that could cause increases in NLR or clinical settings where this marker was used. Secondly, it was not possible to perform a meta-analysis to determine sensitivity, specificity and an optimal cut-off point to improve the estimation of the prognostic value of NLR in patients with testicular cancer. Third, we found high heterogeneity among the included studies, which was traced back to the poor methodological quality in some of these studies.

CONCLUSIONS

High NLR values are associated with worse OS; however, this result had publication bias, and the association was lost when this bias was corrected. Furthermore, no statistically significant association was found between NLR values and PFS. Future studies with large sample sizes that address the prognostic role of NLR with OS and PFS are needed to obtain a more robust conclusion.

SUPPLEMENTARY MATERIALS

The following supplementary information is attached to this article: Appendix 1, Search Strategy; Table S1, Outcome definitions of included studies; Table S2, Newcastle-Ottawa Quality Assessment Scale for included studies; Figure S1, Trim and Fill method of all the studies that evaluated the association between NLR and OS.

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