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Neutrophil/lymphocyte ratio is associated with survival in synovial sarcoma

Dorian Yarih García-Ortega[a,*], Alethia Álvarez-Cano[a], Luis Adolfo Sánchez-Llamas[a], Claudia H.S. Caro-Sanchez[b], Héctor Martínez-Said[a], Kuauhyama Luna-Ortiz[a], Mario Cuéllar-Hübbe[a]

[a] Departent of Surgical Oncology, National Cancer Institute Mexico City, Mexico
[b] Department of Pathology, National Cancer Institute Mexico City, Mexico

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ABSTRACT

Background: Synovial sarcoma is a rare malignant soft tissue tumor, more common in adolescents and young adults and entails a poor prognosis. Several good prognostic factors have been well established such as age less than 25, size less than 5 cm and absence of a poorly differentiated component. Inflammation has a well-established role in tumor proliferation and survival. The aim of this study was to investigate the prognostic significance of the neutrophil/lymphocyte ratio (NLR) in a large cohort of synovial sarcoma patients.
Methods: Retrospective study of 169 consecutive patients. We analyzed the relation of preoperative NLR on disease-free survival (DFS) and overall survival (OS) using Kaplan–Meier curves and Cox proportional models.
Results: Of the 169 patients included, there were 90(53.3%) females and 79(46.7%) males. Median age was 32yo (11–73). Median survival was 34.1 and mean disease-free survival was 21.4 months. Mean tumor size was 12.5 cm (1.2–77 cm). Applying receiver operating curve analysis, we determined a cut-off value of 3.5. In univariate and multivariate analysis, increased NLR was significantly associated with poor OS. A < 3.5 NLR was an independent prognostic factor in all stages ($p = 0.002$).
Conclusions: NLR > 3.5 was found to be a reliable prognostic factor in this cohort. Given its widespread availability, we believe it's use in clinical practice and further clinical trials should be considered.

1. Background

Synovial sarcoma is a malignant soft tissue tumor that may develop in any anatomic site. Most frequent locations are lower limb periarticular areas, and it can be found near tendon sheats, bursas or joint capsules [1,2]. Although microscopically it is similar to developing synovial membrane, there is no evidence to support that it develops from or differentiates into synovial tissue. It's cytogenetic origin has not been elucidated. The original term was a teno synovial sarcoma, given by Hajdu [3]. 5–50% of all sarcomas are synovial type; however its frequency is variable in several series [4,5].

Synovial sarcoma is more common in adolescents and young adults (ages 15–40), it can, however, develop in children less than 10-years old, and there are cases reported in newborns. Males are more frequently affected with a 1.2:1 ratio [6].

Diagnosis is made based on morphologic appearance, immunohistochemistry and cytogenetic findings. Most synovial sarcomas are TLE-1 (transducing-like Enhancer of Split-1) and BLC-2 positive; several citokeratines and epithelial membrane antigen might be positive. Most synovial sarcomas harbor a X; 18 translocation t(X; 18) (p11.2; q11.2) which results in the fusion of the SYT gene from chromosome 18 (18q11) with one of the genes from the X chromosome (Xp11) SSX1, SSX2, or SSX4 [6–8].

Prognosis is poor in patients treated with surgical resection only when margins are not adequate and without adjuvant therapy, in such cases, recurrence is expected in up to 80% of patients. Wide excision and adjuvant radiation therapy may lower local recurrence down to 40% [11]. 5-year overall survival (OS) is 64–76% [12,13] in non-metastatic disease. If distant metastases are present, the prognosis is worse. Several prognostic factors have been well established such as age less than 25, less than 5 cm, and the absence of a poorly differentiated component [9–16].

The link between inflammation and cancer was first discovered by Rudolph Virchow in the 19th century, he first described the presence of leucocytes in malignant tissue. Current knowledge accepts the complex role of inflammation in tumorigenesis, evasion of the immune response

* Corresponding author. Skin and Soft Tissue Tumors Department, *Instituto Nacional de Cancerología*, Av. San Fernando 22, Seccion XVI, 14080, Tlalpan, Mexico City, Mexico.
E-mail addresses: dgarciao@incan.edu.mx, dr_doriangarcia@me.com (D.Y. García-Ortega).

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and other tumor process [17].

Currently, neutrophil/lymphocyte ratio (NLR) has been studied as a prognostic factor in malignant diseases such as melanoma, colorectal, lung and renal cancer. Evidence of NLR in sarcomas is scarce [19]. No study has addressed this association specifically in synovial sarcoma.

The objective of this study was to analyze the prognostic significance of NLR in overall survival in synovial sarcoma patients treated at the National Cancer Institute in Mexico.

2. Material and methods

All patients treated at the National Cancer Institute in Mexico from January 1st, 2005 to December 31st, 2014 with a histologically-proven synovial sarcoma were included. Data were obtained from the electronic clinical record. During the initial routine analyses, all patients had at least one complete blood count performed, we estimated the NLR in the first sample recorded. We recorded basic demographic information, TNM classification and clinical stage (using the 8thEd of the AJCC cancer staging manual), histologic subtype, treatment received and follow up. Data were analyzed using measures of central tendency and dispersion for each variable. The NLR was calculated from the differential leukocyte count by dividing the absolute neutrophil count by the absolute lymphocyte count. The cut-off value was defined according to receiver operating characteristic curve analysis, and a cutoff value of 3.5 was determined (Fig. 1). OS was calculated from the date of first medical evaluation to death or last follow up. Survival curves were calculated by Kaplan-Meier method and analyzed by log-rank test. Statistical analyses Overall survival (OS) and recurrence-free survival (RFS) rates were analyzed using the Kaplan-Meier method and the log-rank test. Univariate and multivariate analyses for OS and RFS were performed using Cox's regression model. A p value less that 0.05 was considered significant. All statistical analyses were performed using the Statistical Package for Social Sciences version 22.0 (SPSS, IBM Corporation, New York, New York, US).

2.1. Ethical considerations

This study was conducted according to the declaration of Helsinki (2008) principles and Mexican Health Guidelines. This is a retrospective study, in which no intervention was performed on the patients, it was approved by the Local Ethics Committee of the National Cancer Institute (Mexico).

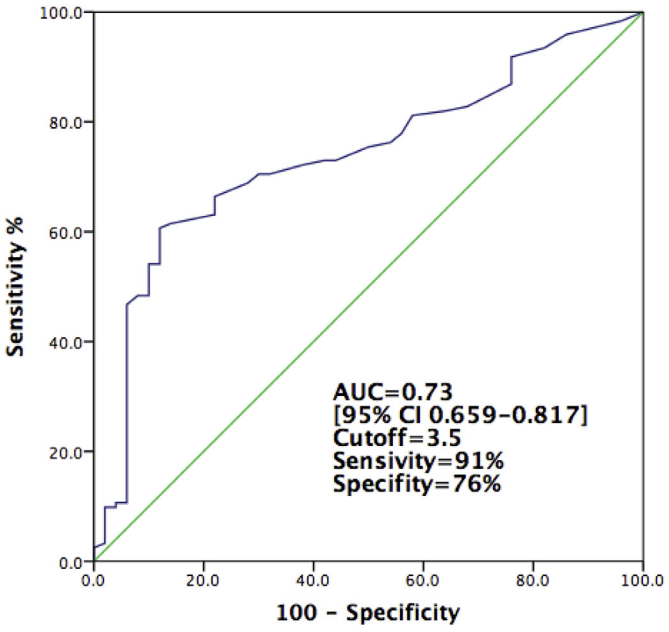

Fig. 1. ROC curve (Area) INL synovial sarcoma.

Table 1
Clinical and demographic characteristics N = 169.

Age	33.7 (11–73)
Male:Female	79:90(46.7:53.3%)
Tumor size	12.5 cm (1.2–77)
Histologic subtype	
Monophasic	140(82.8%)
Biphasic	24(14.2%)
Undifferentiated	2(1.2%)
Others	3(1.8%)
N	
N0	155(91.7%)
N1	14(8.3%)
M	
M0	107(63.3%)
M1	62(36.7%)
Clinical Stage	
II	19(11.2%)
IIIa-IIIb	88(52.1%)
IV	62(36.7%)
Site of distant metastases	
Lung	54 (32%)
Liver	3 (1.8%)
Bone	2 (1.2%)
Multiple sites	2 (1.2%)
Others.	1 (0.6%)
Recurrent disease	
No	90 (53.3%)
Local	17 (10.1%)
Regional	3 (1.8%)
Distant.	48 (28.4%)

3. Results

169 consecutive patients were included for analyses. 90(53.3%) were female and 79(46.7%) were male. Median age was 32 (11–73) years old. Overall median survival was 34.1 months and mean disease-free survival was 21.4 months. Average tumor size was 12.5 (1.2–77) cm. The most common subtype was monophasic in 140 (82.8%) and biphasic in 24 (14.2%). Table 1 shows the demographic characteristics of our cohort. Only 19 patients (11.2%) were stage II. 88 (52.1%) patients presented with stage III disease, and 62 (36.7%) were in stage IV. Extremities were the most common primary site (Table 2).

72 (41.6%) patients were treated with both surgery and radiation therapy, preoperative RT in 1 and postoperative in 62 (35.8%) cases. Surgery alone was the only treatment in 22 patients this due to small tumor size or because they were amputated. Systemic therapy was not given to all patients, the drug of choice, as well as doses, were decided depending on functional status, because of heterogeneity in this variable, we could not perform an analysis on the role of chemotherapy.

Applying receiver operating curve analysis, we determined a cut-off value of 3.5 as optimal to discriminate between survival and death with an AUC = 0.73[95% CI 0.659–0.817] Cutoff = 3.5 Sensivity 91% and Specificity 76% (Fig. 1).

3.1. Prognostic factors of death and recurrence

Univariate analysis was performed to identify recurrence-related factors. No statistically significant difference was found for tumor size (< 5 cm vs. > 5 cm), histological subtype or localization. The use of adjuvant radiation therapy did show a significant difference (p= < 0.001). Lymph node status was also significant for recurrence (p = 0.014). Regarding survival, both overall and specific; neither size, anatomic location, histological subtype, gender or lymph node status were significant. NLR remained an independent prognostic factor in all scenarios (Table 3).