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The derived neutrophil/lymphocyte ratio predicts poor clinical outcome in soft tissue sarcoma patients

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Abstract

BACKGROUND: Inflammation plays an important role in tumor proliferation and survival in cancer patients. The aim of this study was to investigate the prognostic impact of the pre-operative–derived neutrophil/lymphocyte ratio (dNLR) in a large cohort of soft tissue sarcoma (STS) patients after curative surgical resection.

METHODS: The impact of preoperative dNLR on disease-free survival (DFS) and overall survival (OS) in retrospectively evaluated 340 STS patients was assessed using Kaplan–Meier curves and Cox proportional models.

RESULTS: Applying receiver operating curve analysis, we determined a cut-off value of 2.39 for the dNLR to be optimal for discrimination of patients' survival in the whole cohort. Kaplan–Meier curves revealed a dNLR greater than or equal to 2.39 as a marker for decreased DFS ($P = .031$) and OS ($P = .007$, log-rank test) in STS patients. In multivariate analysis, increased dNLR was significantly associated with poor OS (hazard ratio 1.60, 95% confidence interval 1.07 to 2.40, $P = .022$).

CONCLUSIONS: This study demonstrates that preoperative dNLR might represent a well-correlated surrogate marker for the widely validated NLR. The dNLR is easily obtainable and can provide important information for individual risk assessment in clinical trials.

Soft tissue sarcomas (STSs) are a heterogeneous group of tumors that arise predominantly from the embryonic mesoderm.[1] STS has more than 70 distinct histological subtypes, with leiomyosarcoma, liposarcoma, synovial sarcoma, undifferentiated pleomorphic sarcoma, and myxofibrosarcoma being among the most common subtypes.[2]

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STS occurs rarely and accounts for approximately 1% of malignancies in adults and 2% of cancer mortality.[3,4] The treatment of STS is largely dictated by tumor size, histologic grade, histologic subtype, tumor depth and site, and age at diagnosis.[5] Despite improvements in local control rates with wide local resections and radiation therapy, metastasis and death remain a significant problem in 50% of patients who present with high-risk STSs.[1] Patients typically demonstrate a median survival ranging from 11 to 18 months from diagnosis of advanced disease.[6,7] Hence, readily available and economically feasible clinical tools to identify cancer patients at high risk of tumor recurrence and death are required for improving survival data.

Inflammation is a critical component of tumor progression. It is now becoming clear that the tumor microenvironment, which is largely orchestrated by inflammatory cells, is an essential participant in the neoplastic process, promoting proliferation, survival, and migration of tumor cells.[8,9] In recent years, there has been raising interest in the use of systemic inflammatory markers as prognostic factors in malignancies. Particularly, the neutrophil/lymphocyte ratio (NLR) represents a marker of systemic inflammatory response and has been widely reported as a prognostic factor in various types of cancer, including colon cancer, renal cell carcinoma, pancreatic cancer, ovarian cancer, and STS.[10–14] However, in most clinical trials, only white cells and neutrophil counts without specification of the absolute lymphocyte count have been documented. To offer an inflammation-based biomarker for these clinical trials, Procter et al recently developed a so-called derived NLR (dNLR), which consists of neutrophil count divided by (white cell count minus neutrophil count). The authors of this study evaluated the prognostic value of the dNLR on clinical outcome in different cancer types, and demonstrated that the dNLR had similar prognostic value to the well-established NLR.[15] To the best of our knowledge, no study has been previously published with a special focus on the prognostic value of the dNLR in STS patients. Therefore, the aim of this study was to evaluate the prognostic impact of the preoperative dNLR on disease-free survival (DFS) and overall survival (OS) in a large cohort of STS patients to decipher the usefulness of this potential prognosticator in clinical trials.

Patients and Methods

Subjects

Three hundred forty patients with histologically confirmed STS and available laboratory parameters, who have been operated between March 1998 and August 2013 at the Department of Orthopaedic Surgery, Medical University of Graz, were included in this retrospective study. Follow-up was performed until September 2013. All patients were included in the follow-up program of the Department of Orthopaedic Surgery and the Division of Clinical Oncology, Medical University of Graz, providing follow-up examinations in regular intervals (3-month intervals in years 1 to 3, 6-month intervals in years 4 to 5, and 12-month intervals in years 6 to 15 after diagnosis). The laboratory data, including preoperative blood neutrophil and leukocyte count, were obtained by preoperative determination 1 to 3 days before surgery was performed. Follow-up investigations included clinical check-up and radiological analyses (computed tomography alternating with X-ray of the chest, local magnetic resonance imaging, and abdominal ultrasound). Clinicopathological data including histopathological diagnosis and tumor grade were retrospectively obtained from the patient's history. For this study, all histological specimens were centrally reviewed by an independent experienced soft tissue pathologist (B.L.A.). All sarcomas were diagnosed according to the current World Health Organization classification of soft tissue and bone tumors.[2] Tumors were graded according to the French Federation of Cancer Centres Sarcoma Group grading system if possible or tumor grade was defined by tumor entity.[16] Malignant fibrous histiocytomas have been reclassified according to the current diagnostic criteria.[2,17] This study has been approved by the Institutional Review Board of the Medical University of Graz (25-050 ex 12/13).

Statistical analyses

The primary endpoint of this study was OS, which was calculated from the date of diagnosis to the date of death from any cause. The secondary endpoint was DFS (time between diagnosis and local recurrence or distant metastases). We seek an ideal cut-off value for the continuous dNLR by applying receiver operating curve analysis as previously reported.[18] The relationship between dNLR and other clinicopathological parameters was studied by nonparametric tests (chi-square test and Mann–Whitney *U* test). Patients' clinical endpoints were calculated using Kaplan–Meier curves and compared by the log-rank test. Backward stepwise multivariate Cox proportion analysis was performed to determine the influence of age, sex, tumor grade, tumor site and size, and dNLR on DFS and OS. Hazard ratios estimated from the Cox analysis were reported as relative risks with corresponding 95% confidence intervals. All statistical analyses were performed using the Statistical Package for Social Sciences version 20.0 (SPSS, Inc, Chicago, IL). A 2-sided *P* value of less than .05 was considered statistically significant.

Results

Overall, there were 175 male and 165 female patients with STS. Two hundred nineteen patients had grade 3 sarcomas according to the French Federation of Cancer Centres Sarcoma Group grading system, 62 patients were histologically classified as having grade 1, and 59 patients had grade