# Neutrophil to lymphocyte ratio is a strong predictor of tumor recurrence in early colon cancers: A propensity score-matched analysis

**Gennaro Galizia, MD, PhD,[a] Eva Lieto, MD, PhD,[a] Anna Zamboli, MD,[a] Ferdinando De Vita, MD, PhD,[b] Paolo Castellano, MD, PhD,[a] Ciro Romano, MD, PhD,[c] Annamaria Auricchio, MD,[a] Francesca Cardella, MD,[a] Lorenzo De Stefano, MD,[a]** *and* **Michele Orditura, MD, PhD,[b]** *Naples, Italy*

***Background.*** *Systemic inflammation and immune response play a crucial role in tumor growth, and the neutrophil to lymphocyte ratio (NLR) may be a simple way to assess the host inflammatory response. The NLR has been shown to be a prognostic indicator in many human tumors; in early colon cancers, it has been evaluated only in a few studies and its role remains controversial.*

***Methods.*** *We analyzed data from 503 colon cancer patients. The best cutoff value for NLR was defined by receiver operating characteristic curve analysis. We grouped 276 Dukes A/B colon cancers, not receiving adjuvant chemotherapy, into low (<2.36) and high (>2.36) NLR and subjected to further analyses related to disease-free survival (DFS). A propensity score-matched analysis and the inverse probability of treatment weighting (IPTW) were performed to avoid confounding bias.*

***Results.*** *The NLR correlated with tumor stage and oncologic outcome. The best NLR cutoff value was identical in the whole cohort and in Dukes A/B patients. Low NLR patients had a significantly better DFS rate than high NLR patients (hazard ratio [HR], 0.27;* P = *.0001); along with elevated carcinoembryonic antigen levels and Dukes B stage, high NLR was an independent prognostic factor of worse prognosis (HR, 2.86;* P = *.0033). Even in Dukes A patients, NLR discriminated between relapsing and nonrelapsing patients. Propensity score and IPTW analyses confirmed such results, thus excluding possible misinterpretation.*

***Conclusion.*** *Preoperative NLR, an inexpensive and readily available biomarker, can predict tumor relapse and should be assessed for implementation of tailored therapy in early stage colon cancer. (Surgery 2015;158:112-20.)*

*From the Division of Surgical Oncology, Department of Anesthesiological, Surgical and Emergency Sciences,[a] the Division of Medical Oncology, 'F. Magrassi - A. Lanzara' Department of Clinical and Experimental Medicine and Surgery,[b] and the Division of Internal Medicine, Allergy and Clinical Immunology, Department of Medical and Surgical Sciences,[c] Second University of Naples School of Medicine, Naples, Italy*

Colorectal cancer is the third most common malignancy worldwide, accounting for nearly 144,000 new cases and 51,000 deaths in the United States, and approximately 215,000 deaths in Europe[1,2] in 2014. Approximately four-fifths of colorectal cancers are found in the large bowel (colon cancer) and one-fifth in the rectum. Traditionally, the prognosis of colon cancer has been assessed by Dukes classification and tumor–node–metastasis (TNM).[3,4] Early stage colon cancer patients (ie, node-negative tumors classified as Dukes A or B) treated with potentially curative operations are expected to have a good long-term survival and derive no benefit from adjuvant chemotherapy.[5,6] However, 10–20% of these patients ultimately succumb to recurrent disease, indicating that the conventional staging procedures may be unable to predict precisely cancer prognosis.[7,8] This leaves space for the development

G.G. and E.L. contributed equally to this work.

No source of financial support.

Accepted for publication February 22, 2015.

Reprint requests: Gennaro Galizia, MD, PhD, Division of Surgical Oncology, Department of Anesthesiological, Surgical and Emergency Sciences, Second University of Naples School of Medicine, c/o II Policlinico, Edificio 17, Via Pansini, 5, 80131 Naples, Italy. E-mail: gennaro.galizia@unina2.it.

0039-6060/$ - see front matter



http://dx.doi.org/10.1016/j.surg.2015.02.006

of supplementary biomarkers able to select node-negative colon cancers with a high risk of tumor recurrence, which may benefit from adjuvant treatments.[9]

Robust evidence suggests that oncologic outcome is influenced not only by tumor behavior, but also by host response through systemic inflammation.[10,11] Blood parameters reflecting inflammation, such as hypoalbuminemia, elevated C-reactive protein, and increased levels of some cytokines, as well as tumor microenvironment, have been extensively investigated as novel biomarkers in several human cancers, including colon cancer, with conflicting results.[12-14] However, cell-mediated immunity may be simply reflected by the lymphocyte count, whereas systemic inflammation may be suggested by neutrophilia.[9] Consequently, neutrophil to lymphocyte ratio (NLR), calculated as the neutrophil count divided by the lymphocyte count, may be an indicator of the type of host response to the tumor. In recent years, several studies have shown that a high NLR correlates with advanced stage and poor prognosis in a variety of human tumors, including liver, pancreatic, and gastric cancers.[9,15] In particular, NLR values from 3 to 5 have been associated with a worse outcome in colorectal cancer patients; thus, preoperative NLR assessment may allow further insights into the optimal treatment strategy for early stage colon cancer.[16,17] However, because of variance in study design, use of heterogeneous patient groups, different cutoff values, and controversial results, the direct impact of NLR on outcome of such patients remains inconclusive.[9,15,18]

The aim of this study was to evaluate how NLR correlates with other prognostic indicators in a large series of colon cancer patients undergoing surgery. In particular, the utility of NLR as a prognostic indicator in node-negative colon cancer patients undergoing potentially curative surgery was investigated in an effort to identify high-risk patients who may benefit from adjuvant treatments. The propensity score-matched analysis was carried out to avoid risk of confounding bias[19]; in addition, because a smaller number of matched couples may derive from such an analysis, computation of the adjusted Kaplan–Meier estimator, including all patients, was added.[20]

## PATIENTS AND METHODS

We identified 708 patients undergoing operation for sporadic colorectal cancer from July 1994 to June 2014 at a single unit of surgical oncology. Rectal cancers (164 cases) were primarily excluded because their molecular features, preoperative and postoperative treatments, recurrence rate, and overall survival can differ greatly from other large bowel carcinomas, thus possibly causing misinterpretation of results.[21] Forty-one patients with alterations of the white blood cell count owing to concomitant infectious diseases, autoimmune diseases, or other recognizable inflammatory conditions, as well as being operated on in an emergency setting owing to complications, were excluded. For the remaining 503 patients, we collected the following data: age, gender, tumor site (right and left colon by using middle transverse colon as partition), basal carcinoembryonic antigen (CEA) serum level, performance status according to the Eastern Cooperative Oncology Group (ECOG) scale, postoperative morbidity (complications were defined as grade II or higher of the Clavien-Dindo classification),[22] degree of histologic differentiation (well, moderate, or poor), TNM stage,[4] Dukes stage,[3] tumor size, number of resected nodes, number of metastatic nodes, lymph node ratio (the ratio between metastatic and resected nodes), radicality (defined as the removal of all of the macroscopic tumoral tissue, absence of microscopic residual tumor, and free resection margins at postoperative pathologic examination), recurrence rate, and overall and disease-free survival (DFS) rates. The NLR was calculated using standard laboratory blood test results performed before any diagnostic procedure or surgery to avoid unspecific changes in white blood cell counts. Our standardized follow-up protocol includes a 3-monthly clinical assessment for the first 2 years, followed by biannual surveillance until year 5. Abdominal ultrasonography is performed every 6 months; colonoscopy and chest and abdominal CT are undertaken every year. If recurrence is suspected, patients undergo further diagnostic testing, complemented by routine histopathologic examination of a biopsy specimen. No patient was lost to follow-up, which was completed through December 31, 2014. All patients gave their informed consent and the study was approved by the Department of Anesthesiological, Surgical and Emergency Sciences of the Second University of Naples.

Statistical analysis was carried out using the SPSS statistical package (SPSS Inc, Chicago, IL) integrated by the Medcalc software version 9.4.2.0 (Mariakerke, Belgium). Continuous data are expressed as mean ± standard deviation, range, and median values. The equality of group means was analyzed by unpaired Student's $t$ test. Because the aim of this study was to individuate factors related