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Neutrophil to Lymphocyte Ratio as Predictor of Surgical Mortality and Survival in Complex Surgery of the Upper Gastrointestinal Tract

Karen Y. Jaramillo-Reta, Magali E. Velázquez-Dohorn and Heriberto Medina-Franco*

Department of Surgery, Section of Surgical Oncology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México, D.F., Mexico

ABSTRACT

Background: Neutrophil-lymphocyte ratio (NLR) has been proposed as a marker of inflammatory response and as a prognostic tool in surgical procedures. **Objective:** To evaluate the role of high preoperative NLR (> 4.5) as predictor of morbidity and mortality in patients with upper gastrointestinal tract resection, and survival in cancer patients. **Methods:** Retrospective study of patients undergoing upper gastrointestinal tract surgery from 2007 to 2012. Variables associated with morbidity, mortality, and survival were analyzed. Univariate and multivariate analyses were performed. Significance was considered at $p < 0.05$. **Results**: 548 patients were included. The most common surgical procedures were Whipple (44.3%) and gastrectomy (30.7%). Surgical morbidity was 40.5% and mortality 6.4%. Factors associated with significant surgical complications were: low body mass index, AJCC stage ≥ III and ASA ≥ III. Factors associated with mortality were older patient age, high NLR, AJCC stage ≥ III, ASA ≥ III, blood transfusion and Charlson > 4. On multivariate analysis, only high NLR and Charlson > 4 remained significant. High NLR was significantly associated with reduced survival in patients with malignant neoplasms (three-year survival 76.1 vs. 65.7%; $p = 0.04$). **Conclusion**: High preoperative NLR appears to be a biomarker to predict surgical mortality and survival in patients undergoing complex surgery of the upper gastrointestinal tract. (REV INVES CLIN. 2015;67:117-21)
Corresponding author: Heriberto Medina-Franco, herimd@hotmail.com

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BACKGROUND

Inflammation is a critical component in the development and progression of neoplasia due to the interaction between proinflammatory cytokines[1,2] and other pathways involving nuclear factor kappa B (NFkB) and signal transducers and activators of transcription (STAT)[3,4]. There are several physiological and pathological processes in which the inflammatory response contributes to the development of cancer; however, other components are associated with its development, including growth factors, stroma-activated cells, cell proliferation-promoting agents, and sustained DNA damage[5,6].

Corresponding author:
*Heriberto Medina-Franco
Department of Surgery
Instituto Nacional de Ciencias Médicas y Nutrición
Salvador Zubirán
Vasco de Quiroga, 15
Col. Sección XVI. Del. Tlalpan
C.P. 14000, México, D.F., México
E-mail: herimd@hotmail.com

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To determine the prognostic value of the systemic inflammatory response, different markers have been evaluated, such as cytokines, serum albumin, C-reactive protein (CRP), modified Glasgow prognostic score, absolute leukocyte count, neutrophil-lymphocyte ratio (NLR), and lymphocyte-platelet ratio, among others[7]. These have been found to be prognostic factors for survival and development of complications in preoperative settings[8], although in some cases they are not associated with prognosis after surgical resection[9].

Recent studies have highlighted the use of high preoperative NLR as a poor prognostic factor for postoperative patient outcome[10,11]. There is evidence, mostly from retrospective studies, in which a NLR <4.5 was shown to be a predictor of survival in patients with mesothelioma or sarcoma undergoing systemic therapy[12,13] and it has been found to be a marker of response to chemotherapy and predictor of survival in advanced colorectal cancer[14]. A NLR > 2.5 is used as a biomarker for detection of incidental papillary thyroid microcarcinoma[15]. Similarly, a NLR > 4 was an indicator of survival and mortality in unresectable pancreatic adenocarcinoma[16,17], gastric or esophageal cancer[18-20], in patients with completely resected non-small cell lung cancer[21,22], and a prognostic factor for five-year mortality in breast cancer[23]. In a recent meta-analysis, a high NLR was associated with adverse overall survival in many solid tumors[24].

The NLR has been associated with morbidity in benign conditions as well[25,26]. In Mexico, there are no studies to our knowledge that analyze the impact of NLR on surgical morbidity and mortality in patients who underwent surgery of the upper gastrointestinal tract, and the information in the literature is scarce since most of the evidence is related to the impact of this ratio on long-term prognosis. The purpose of this study was to evaluate the role of preoperative NLR as a predictor of morbidity and mortality in patients who undergo complex surgery of the upper gastrointestinal tract, as well as survival in patients with malignant neoplasms in these locations.

METHODS

Subjects

A retrospective study of patients who underwent complex upper gastrointestinal surgery from January 2007 to December 2012 was conducted at the National Institute of Medical Sciences and Nutrition, a referral center in Mexico City. A total of 548 patients were studied, 397 (72.4%) with a histopathological diagnosis of cancer. Patients with hematological disorders or active infections were excluded due to possible alterations in preoperative baseline white blood cell counts. Data on laboratory studies and pathology reports were taken from the medical records.

The white blood cell count was routinely performed within one week before the surgical procedure. The NLR values were calculated by dividing the total neutrophil count by the total lymphocyte count, and a NLR > 4.5 was considered high. Comorbidities were evaluated using the Charlson score[27]. Postoperative complications occurring within 30 days of the surgical procedure and evaluated according to Clavien-Dindo classification[28] were obtained from the medical charts. Survival status was obtained from the last clinical note of follow-up in the hospital records.

Elderly patients were considered as those ≥ 70 years old; obesity was defined as body mass index (BMI) > 30, and malnutrition as BMI < 18. Anemia was defined as hemoglobin < 12 g/dl and hypoalbuminemia as serum albumin < 3 g/dl. Blood transfusion was ≥ 250 ml.

Statistical analysis

Variables associated with morbidity and mortality were analyzed using chi square test for categorical variables and Student's *t* test for continuous variables. Survival was calculated with the Kaplan-Meier method and curves were compared with the log-rank test. Multivariate analysis was performed with Cox regression analysis. Statistical significance was considered at $p < 0.05$. Analyses were performed using SPSS for Windows, v19.0 (IBM Corporation 2010, Somers, NY, USA).

RESULTS

A total of 548 patients were included, 52.9% women and 47.1% men, with a mean age of 53 years (range, 18-91). The most common patient comorbidities are shown in table 1. From the total cohort, 397 patients (72.4%) had a histological diagnosis of cancer and the most common malignancies were: gastric adenocarcinoma (26.7%), pancreatic adenocarcinoma (23.1%),

Table 1. Patient comorbidities

	(n)	%
Diabetes mellitus	137	25.0
Arterial hypertension	124	22.6
Anemia	77	14.0
Peptic ulcer disease	47	8.5
Dyslipidemia	42	7.6
Osteoarthritis	14	2.5
Chronic obstructive pulmonary disease	13	2.3
Benign prostatic hyperplasia	13	2.3
Peripheral venous insufficiency	12	2.1
Low body mass index	11	2.0

Table 2. Surgical procedures

Procedure	(n)	%
Whipple	243	44.3
Gastrectomy	168	30.7
Distal pancreatectomy	76	13.9
Esophagectomy	45	8.2
Other	14	2.6

Table 3. Surgical morbidity

	(n)	%
Sepsis	135	24.6
Nausea and vomiting	38	6.9
Fistula	28	5.1
Pneumonia	26	4.7
Septic shock	22	4.0
Steatorrhea	16	2.9
Diarrhea	16	2.9
Fever	15	2.7
Upper gastrointestinal bleeding	15	2.7

adenocarcinoma of the ampulla of Vater (16.6%), and neuroendocrine tumor (9.5%). The main diseases of the remaining 151 patients were: pancreatic cyst (49%), chronic pancreatitis (15.2%), and caustic esophageal stenosis (10%). The most common surgical procedure was Whipple (44.3%) followed by gastrectomy (30.7%); other surgical procedures are shown in table 2.

Surgical morbidity was 40.5% and mortality 6.4%. The most common medical and surgical complications are depicted in table 3. Factors associated with significant surgical complications (Clavien ≥ 3) were: low BMI (p = 0.004), American Joint Committee for Cancer (AJCC) stage ≥ III (p = 0.049) and American Society of Anesthesiologists (ASA) ≥ III (p = 0.008). Factors associated with surgical mortality were older age (p = 0.001), high NLR (p = 0.0001), AJCC stage ≥ III (p = 0.0001), ASA ≥ III (p = 0.0001), blood transfusion (p = 0.003) and Charlson ≥ 4 (p = 0.043).

On multivariate analysis only a high NLR (OR: 1.35; 95% CI: 1.2-3.4; p = 0.02) and Charlson > 4 (OR: 1.2; 95% CI: 1.1-4.6; p = 0.045) retained statistical significance.

The following variables were associated with better survival: NLR < 4.5 (p = 0.014), younger age (p = 0.0001), and AJCC stage < III (p = 0.0001). On multivariate analysis only tumor stage retained statistical significance (AJCC < III, OR: 0.40; 95% CI: 0.2-0.8; p = 0.001). The NLR lost its statistical significance in multivariate analysis. In patients with cancer, the mean survival of those with a NLR > 4.5 was 75 months (95% CI: 61-88), and 85 months (95% CI: 78-93) for those with NLR < 4.5. Overall three-year survival was 65.7 and 76.1%, respectively (p = 0.04).

DISCUSSION

Different biochemical and hematological markers have been used to quantify the impact of the systemic inflammatory response on outcomes in cancer patients: elevated CRP concentration, increased white cell, neutrophil, and platelet counts and hypoalbuminemia. Several inflammation-based prognostic scores for cancer have also derived from combinations of these factors. Among these, the Glasgow prognostic score (GPS), platelet/lymphocyte ratio, and NLR have been assessed. Increased NLR was originally described as a predictor of poor outcome in a Slovakian study of critically ill patients[29]. Since then, most studies have evaluated the role of these inflammatory markers on long-term outcome in cancer patients. Recent studies suggest that the NLR is a good independent indicator to evaluate the condition of a tumor-bearing host and survival in patients with advanced cancer[30]. A NLR cutoff of > 4.5 was able to identify patients with higher risk of progression and death[31].

In our study, most patients (72.4%) had a diagnosis of cancer, and in this subgroup a high NLR was a predictor of long-term survival, although it lost its significance in multivariate analysis probably due to the small sample size. The NLR was a predictor of survival in cancer

patients in addition to age and tumor stage, two very well recognized prognostic factors in cancer patients. The relationship between this marker of systemic inflammatory response and outcome in our series confirms the results of several other studies performed in cancer patients[18-23], and of a recent meta-analysis of patients with solid tumors[24]. There are several mechanisms proposed to explain the relationship between cancer prognosis and inflammatory response, including the release of granulocyte colony-stimulating factor by tumor cells and cancer inflammation through the release of interleukin-1 (IL-1) and tumor necrosis factor-alpha[32]. Relative neutrophilia increases the number of inflammatory markers that include pro-angiogenic factors (vascular endothelial growth factor), growth factors (CXCL8 protein, also known as IL-8), proteases (tissue inhibitors of metalloproteinase) and anti-apoptotic markers (NFkB) that support tumor growth and progression[33]. Although neutrophils have anti-tumor effects, the increased number of neutrophils and lymphocytes are less efficacious.

On the other hand, lymphocytopenia represents a significant decline in the cell-mediated immune system, demonstrated by the marked decrease in T4 helper and T8 suppressor lymphocytes. Systemic inflammation triggered by malignant cells results in the release of a number of immune modulators such tumor growth factor-beta, IL-10 and CRP, which impair lymphocyte action[34]. Natural killer cell activity is repressed when the NLR is high; this would diminish the cell-mediated immune response even further[35]. These responses have direct and indirect interactions with the primary tumor to stimulate angiogenesis and extracellular matrix remodeling[36]. Consequently, it is possible that pre-surgical neutrophilia and lymphocytopenia numbers indicate the level of inflammation related with the tumor and thus predict tumor growth and progression. The magnitude of the inflammatory response to cancer is directly prognostic of long-term outcomes in patients undergoing curative-intent surgery for solid tumors[37]. Therefore, this index was recently demonstrated to be superior to other inflammatory markers in other neoplasms as a prognostic factor. This preoperative marker is widely available, inexpensive, does not require arterial blood gas or extended biochemistry, and is a part of the routine preoperative work-up. We chose to look at the role of NLR as a marker of systemic inflammatory response because preoperative white blood cell count is routinely performed, contrary to CRP or serum albumin, which have been reported to be other markers of systemic inflammation. Measurement of more specific markers of inflammation, such as interleukins or subpopulations of T lymphocytes, is not practical for routine clinical use so we considered the NLR to be an indirect and unspecific but very useful marker for routine clinical use. A challenge remains to identify the optimal cut-off of NLR for predicting outcomes, ranging between 2.2 and 5.0[24]. We chose 4.5 because this value has been used for most studies performed in patients with cancer of the upper gastrointestinal tract[19,20].

In addition to prognosis on cancer patients, the NLR has been reported to be a predictor of long-term outcome in benign conditions like coronary revascularization[25] and even recurrence of atrial fibrillation after cryoablation[38]. The role of this inflammatory marker in short-term outcomes has been scarcely studied. The original description of NLR was done to predict prognosis in critically ill patients[29]; however, there is only one other report looking at the role of this marker in short-term outcome after abdominal surgery for benign conditions[26]. In our study, NLR was a predictor of outcome at 30 days, six months, and 12 months after emergency abdominal surgery in elderly patients, and was found to be a better predictor of prognosis than CRP. To our knowledge, this is the only study reporting NLR as a predictor of 30-day postoperative complications in addition to other well recognized risk factors for surgical morbidity including malnutrition (low BMI), high ASA score or severe comorbidities (Charlson > 4), blood transfusion, and advanced tumor stage in cases of cancer surgery. In addition, only high NLR and Charlson comorbidity score were independent predictors of surgical mortality. This result needs to be confirmed in other larger series, but the NLR appears to be a very simple, inexpensive, and easily available marker to predict surgical complications instead of more complex scoring systems such as APACHE or P-POSSUM, which require postoperative data for their calculation[26].

In conclusion, the results of this study support the use of high preoperative NLR as a biomarker to predict surgical morbidity and mortality in patients who undergo complex surgery of the upper gastrointestinal tract. It also confirms the importance of a chronic systemic inflammatory response influencing long-term clinical outcomes in cancer patients.

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