The Role of Baseline Inflammatory Response Biomarkers in Predicting the Prognosis in No Metastatic Gastric Cancer Patients Treated with Preoperative Chemoradiation

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Abstract

Purpose: To evaluate the prognostic potential of inflammatory response biomarkers neutrophil to lymphocyte ratio (NLR), derived neutrophil to lymphocyte ratio (dNLR), platelet to lymphocyte ratio (PLR) and lymphocyte to monocyte ratio (LMR) in predicting the outcome of gastric cancer patients undergoing neoadjuvant chemoradiation prior to surgical resektion.

Methods: Patients with localized, gastric adenocarcinoma received two cycles of induction chemotherapy of fluorouracil, docetaxel, and cisplatin (TPF) followed by 45 Gy of radiation and concurrent fluorouracil plus docetaxel then surgery for non-metastatic patients. Baseline NLR, dNLR, PLR and LMR calculated from peripheral blood cell count taken at pre-operation were compared with clinicopathological parameters. The prognostic value of baseline NLR, dNLR, PLR and LMR for disease free survival (DFS) and overall survival (OS) were assessed using Log rank and Cox regression.

Results: The final analysis included 80 patient who had resection after neoadjuvant chemoradiation. The receiver operating curve (ROC) cut off values of baseline NLR, dNLR, LMR and PLR in predicting outcome were 2.4, 1.7, 5.1 and 130 respectively. Elevated NLR, dNLR, PLR, LMR, age of patients (≥ 50 years), stage III, grade 3 tumors, R1 resection and partial response to preoperative chemoradiation course with >10% residual tumor were significantly associated with decreased OS, and DFS. Multivariate analysis revealed that elevated NLR and dNLR were independent factors for worse OS and DFS hazard ratio (HR) 2.04 (95% CI=2.41-8.24), 6.63 (95% CI, 1.61-10.32) and DFS with (HR) 1.84 (95% CI=3.27-7.36), 4.63 (95% CI=3.61-12.12) respectively.

Conclusion: The baseline NLR, dNLR, LMR and PLR showed a significant association with different clinicopathological prognostic factors in gastric cancer patients receiving preoperative chemoradiation. Additionally, NLR, dNLR may be considered as potential independent prognostic indicators of clinical outcomes in this group of patients.

Keywords: Inflammatory response; Biomarkers in gastric cancer

Introduction

Gastric cancer is accounting for about 8% of all cancers and 10% of cancer-related deaths [1]. The overall 5-year survival rate is 35% or less for stage II and beyond due to local relapses or metastasis after resection of primary gastric cancer. These sobering results have initiated efforts to improve the treatment results for this group of patients using adjuvant (postoperative) or neoadjuvant (preoperative) radiation therapy and/or chemotherapy [2-4]. The survival benefit from postoperative chemoradiotherapy after complete resection of gastric cancer is supported by at least three randomized trials [5-8]. The postoperative chemoradiotherapy has been established as a standard approach for completely resected gastric cancer by the INT0116 study Moreover, at least three trials have compared perioperative chemotherapy with surgery alone [9-11]. In the MAGIC trial patients with potentially resectable gastric were randomly assigned to surgery alone or surgery plus perioperative chemotherapy (three preoperative and three postoperative cycles of epirubicin, cisplatin, and infusional 5-fluorouracil) [9]. Only 42% were able to complete treatment, including surgery and all three cycles of the postoperative chemotherapy. These data emphasize one of the major problems with the perioperative approach, which is the difficulty in administering the full number of postoperative chemotherapy cycles. The preoperative chemoradiotherapy strategy provides an additional potential advantage as location of the primary cancer is known more precisely, which would facilitate the planning of more accurate and effective radiation fields. It also provides a window of observation for more advanced cancer to manifest itself before a major operation is undertaken [12-14]. Moreover, the heterogeneous prognosis among gastric cancer patients necessitated the seek of effective biomarkers for the early detection and outcome prediction. Recently, chronic inflammation was found to plays a critical role in the initiation and progression of numerous cancers, including gastric cancer [15,16]. Interestingly, cancer cells can recruit and activate various leukocytes (especially neutrophils and monocytes) by T cells, specific chemokines and prostaglandins [17-20]. Moreover, the activation of platelet stimulated by proinflammatory cytokines participates in neutrophil recruitment and promotes inflammatory response [21]. The inflammatory response to tumor may contribute to

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tumor growth, progression and metastasis through several mechanisms, including the up-regulation of inflammatory mediators and cytokine, aberrant activation of immune regulatory cytokines, suppression of apoptosis, and DNA damage [22]. Those inflammatory biomarkers in the peripheral blood are considered as potential predictive markers for cancer prognosis. In recent years, several indicators derived from the peripheral blood such as the neutrophil to lymphocyte ratio (NLR), derived neutrophil to lymphocyte ratio (dNLR), platelet to lymphocyte ratio (PLR) and lymphocyte to monocyte ratio (LRM) have been widely investigated as useful prognostic indicators in various kinds of cancers including gastric cancer, colorectal cancer, hepatocellular carcinoma, non-small cell lung cancer, breast cancer and pancreatic cancer [23-27]. However, only one or two inflammatory biomarkers have been evaluated for the prognosis of patients with gastric cancer according to previous reports [11,17-21]. Moreover, the optimal cut-off values of the biomarkers from these studies were still inconsistent. Consequently, further study on the prognostic values of these biomarkers in patients with gastric cancer is necessary. This study aimed to evaluate the prognostic potential of NLR, dNLR, PLR and LMR biomarkers in predicting the outcome of gastric cancer patients undergoing neoadjuvant chemoradiation prior to surgical resection.

Materials and Methods

Retrospective review of gastric cancer patients treated or referred to Clinical Oncology department Alexandria University and Surgical Oncology Department National Cancer Institute Cairo University between January 2012 and December 2015 after obtaining Institutional Board Approval (IRB) approval. All patients signed informed consent. Medical records were reviewed to select non metastatic gastric cancer patients who received neoadjuvant chemoradiation prior to surgical resection that consisted of two 28-day cycles of induction chemotherapy and then chemoradiotherapy and determine known prognostic variables including: age, histology, grade, surgical stage, response to neoadjuvant chemoradiation, in addition to the tested pretreatment prognostic biomarkers neutrophil count to lymphocyte count (NLR), derived neutrophil to lymphocyte ratio (dNLR) was constructed as follows: dNLR=neutrophil count to (white cell count-neutrophil count), platelet to lymphocyte ratio (PLR) and lymphocyte to monocyte ratio (LRM) were calculated from peripheral blood cell count which were calculated from peripheral blood count.

Inclusion criteria

Nonmetastatic, localized, histologically proven T1, N1-2, and T2-3, N0-3 gastric or gastroesophageal adenocarcinoma gastric cancer patient. 2-Induction chemotherapy consisted of fluorouracil 750 mg/ m2/day by continuous i.v. infusion on days 1 to 5, cisplatin 20 mg/m2/day on days 1 to 5 and docetaxel 75 mg/m2. Chemoradiation started ≥ 28 days of these induction cycle.

A total dose of 45 Gy (25 fractions of 1.8 Gy) over 5 weeks using at least a 6-MV photon linear accelerator and the three-dimensional conformal radiotherapy technique. Concurrent chemotherapy consisted of fluorouracil at 300 mg/ m2/day by continuous infusion 5 days each week plus docetaxel 20 mg/m2 intravenously weekly for 5 weeks. 3-Only patients with R0 resection were included. R0 resection was defined as removal of all gross tumor and histopathologic examination of proximal, distal, and circumferential margins that revealed the absence of malignant cells more than 2 mm from the edge. The type of operation depended on the location and extent of the primary tumor. For distal cancers, a subtotal gastrectomy while total gastrectomy or esophagogastrectomy was performed for proximal cancers. Lymph node dissection included removal of perigastric lymph nodes (D1) and those along the named vessels of the celiac, modified (D2) lymphadenectomy without (pancreatectomy and splenectomy) with the goal of examining 15 or greater lymph nodes. 4-Post-operation estimated life expectancy ≥ 3 months. 5) No hematology disease, infection, hyperpyrexia and gastroobrosis.

Exclusion criteria

1) Patients who develop evidence of distant metastasis during induction phase were not eligible for surgical resection. 2) Patients with R2 resection (gross residual), or M1 carcinoma.

Patient Follow-Up

After operation, each patient was followed up regularly until December 2015 or until death (every 3 months for the first 2 years and then every 6 months up to 5th year). Physical examination, endoscopy, laboratory tests and imaging were conducted at every visit. The follow-up periods varied from 3 months to 50 months, with a median of 25 months. Overall survival (OS) was calculated from diagnosis to death. For drop-out patients, the date of the last follow-up was applied. Disease-free survival (DFS) was calculated from surgery to disease relapse or until the date of last follow-up.

Statistical Consideration

The impact of different clinical parameters on Baseline response inflammatory biomarkers (NLR, dNLR, LMR and PLR) were evaluated by Mann-Whitney U test (between 2 groups) or Kruskal- Wallis test (≥ 3 groups). Receiver operator characteristic (ROC) curves were used to identify potential Baseline response inflammatory biomarkers cutoffs values in gastric cancer patients treated with neoadjuvant concurrent chemoradiation prior to surgical resection. An area under the curve of 1.0 would indicate a perfect test, whereas 0.5 would represent a noninformative test. Kaplan-Meier method was accessed for survival analysis. Prognostic variables identified by univariate analysis, with P<0.1, were analyzed in the multivariate Cox model. All reported P-values were two-sided. Statistical significance levels were set at P<0.05. Disease free survival (DFS) and overall survival (OS) were calculated using the Kaplan Meier analysis. Log-rank test and Cox regression analysis were performed to correlate the various clinical and pathological parameters to treatment outcomes. All analyses were performed using SPSS 16.0 package program. (SPSS, Chicago, IL)

Results

The final analysis included 97 gastric cancer patients who received neoadjuvant chemoradiation. The final analysis included 80 patients who had resection after neoadjuvant chemoradiation with 56 (70%) male and 24 (30%) female patients aged from 39 to 69 (the median age was 51 years). With regards to histological type, the number of papillary, tubular, poorly differentiated, mucinous and signet ring cell carcinoma were 4 (5%), 17 (21.2%), 40 (50%), 12 (15%) and 7 (8.8%), respectively. Based on the seventh edition of the TNM-UICC/AJCC classification, the number of stage IIA, IIB and IIIA were 32 (40%), 40 (50%) and 8 (10%), respectively. Additionally, the median values of baseline NLR, dNLR, LMR and PLR were 3.12, 2.31, 3.97 and 139 respectively. All patients baseline characteristics are presented in Table 1.

The local optimal thresholds for NLR, dNLR, PLR and LMR

The Receiver Operating Characteristic (ROC) curve, using DFS as the end-point for NLR, dNLR, PLR and LMR (Figure 1). The receiver operating curve (ROC) demonstrated a baseline NLR and
dNLR of 2.4 and 1.7 cut off for predicting DFS (area under the curve: 0.695 and 0.585 with a sensitivity of 71.2%, 68.2% and a specificity of 69.1%, 60.2% respectively). Additionally, the best cut-off value for LMR and PLR were 5.1, 130 respectively. Patients were subsequently divided into two groups according to the optimal cut-off levels, with the high group ≥ the optimal cut-off levels and the low group < the optimal cut-off levels.

Our results revealed that NLR, dNLR, PLR and LMR were significantly associated with tumor stage, depth of invasion, lymph node, histological types and tumor grade respectively. Moreover, PLR had significant correlation with the sex of patients. On the contrary, NLR, dNLR and LMR were not associated with the age of patients. Those patients with tumor stage III-IV, depth of invasion T3-T4, and lymph node N1-N3 had a higher NLR, dNLR, LMR and PLR than those with tumor stage I-II, depth of invasion T1-T2, and lymph node N0 (Table 2).

**Surgical procedure and postoperative pathology**

Ninety-seven patients were assessed for surgery. Eighty patients (82.4%) had a gastrectomy, and 68 patients (85%) had an R0 resection, whereas 12 patients (15%) had R1 resection. Gastrectomy was not done in the remaining six patients due to distant metastasis (six with unsuspected peritoneal carcinomatosis) discovered at surgery. A path CR was noted in both primary tumor sites and associated regional lymph nodes in 18 patients (22.5%) while a path PR in the form of less than 10% residual viable tumor was noted in 13 patients (16.2%). Moreover, 23 patients (28.7%) had from 10 to 50% residual disease in postgastrectomy pathology. On the other hand, 12 patients (15%) had more than 50% residual tumor in their surgical specimens. Thus, the overall pathologic response rate was achieved in 66 patients (82.5%) while the remaining 14 patients had stable or progressive disease after concurrent chemoradiation. In the 80 patients who had a gastrectomy, the primary carcinoma was T3 in 23 patients (28.7%), T2 in 16 patients (20%), T1 in 21 patients (26.3%), and T0 in 20 patients (25%). Twentyseven (33.8%) of the 80 patients who underwent gastrectomy had N0 cancer, 41 patients (51.2%) had N1 cancer, and 12 patients (15%) had N2 cancer (Table 3). The median number of nodes examined in the 80 gastrectomy specimens was 19 (range, 6 to

| Characteristic | No. of patients | % |
|----------------|-----------------|---|
| Age, years | | |
| Median | 51 | - |
| Range | 39-69 | - |
| Sex | | |
| Male | 56 | 70% |
| Female | 24 | 30% |
| Zubrod performance scale | | |
| 0 | 36 | 45% |
| 1 | 38 | 47.50% |
| 2 | 6 | 7.50% |
| Primary site | | |
| Pylorus | 26 | 32.50% |
| Cardia | 18 | 22.50% |
| Fundus | 16 | 20% |
| Body | 12 | 15% |
| Gastroesophageal junction | 8 | 10% |
| Histopathological type | | |
| Papillary | 4 | 5% |
| Tubular | 17 | 21.20% |
| Poorly differentiated | 40 | 50% |
| Mucinous | 12 | 15% |
| Signet ring | 7 | 8.80% |
| Tumor grade | | |
| G1 | 2 | 2.50% |
| G2 | 28 | 35% |
| G3 | 50 | 62.50% |
| N stage | | |
| T1 | 16 | 20% |
| T2 | 20 | 25% |
| T3 | 44 | 55% |
| N0 | 18 | 22.50% |
| N1 | 48 | 60% |
| N2 | 14 | 17.50% |
| Stage group | | |
| II A | 32 | 40% |
| II B | 40 | 50% |
| III A | 8 | 10% |

**Table 1:** Patient Characteristics at baseline (N=80).

| Inflammatory response biomarkers | | |
|-----------------|-----------------|---|
| NLR | | |
| Median | 3.12 | -- |
| <2.4 | 27 | 33.80% |
| ≥ 2.4 | 53 | 66.20% |
| dNLR | | |
| Median | 2.31 | -- |
| <1.7 | 32 | 40% |
| ≥ 1.7 | 48 | 60% |
| LMR | | |
| Median | 3.97 | -- |
| <5.1 | 49 | 61.20% |
| ≥ 5.1 | 31 | 38.80% |
| LMR | | |
| Median | 130 | -- |
| <130 | 33 | 41.30% |
| ≥ 130 | 47 | 58.70% |

Figure 1: Optimal cut-off levels for NLR, dNLR, PLR and LMR were applied with ROC curves for cancer specific survival.
Clinical factors associated with path CR

Many clinical factors were tested for their impact on achieving pathological complete response such as sex, cancer location, histopathological type, baseline T stage, and baseline N stage. The histopathological type (P=0.04), the baseline T stage (P=0.003), N stage (P=0.002), in addition to inflammatory response biomarkers NLR (P=0.001), d NLR (P=0.0024), LMR (P=0.001) and PLR (P=0.003) were significantly associated with path CR (Table 4) and any pathologic response.

The association between baseline characteristics and clinical prognosis

The median follow-up period was 25 months. During the follow-up period, 46 (57.5%) patients were detected as local recurrence or distant metastasis. Among them, 42 (52.5%) patients were dead from cancer-
related disease. The median of DFS and OS was 20 months and 25 months, respectively. Moreover, the 3-year overall survival and disease-free survival were 47.5% and 42.5% respectively (Figures 2 and 3).

To evaluate the association of baseline characteristics with clinical prognosis, Kaplan-Meier survival analysis and log-rank tests were performed. Our results indicated that partial response to preoperative chemoradiation course with >10% residual tumor (Figure 4), NLR (≥ 2.4) (Figures 5 and 6), dNLR (≥ 1.7) (Figures 7 and 8), PLR (≥ 130), LMR (≥ 5.1), age of patients (≥ 50 years), depth of invasion T3, lymph node N1-N3, stage III, grade 3 tumors, R1 resection and partial response to preoperative chemoradiation course with >10% residual tumor were significantly associated with decreased OS, and DFS (Table 5). Cox regression multivariate for overall survival revealed that higher baseline NLR, dNLR along with advanced TNM stage at diagnosis and partial response with >10 residual tumor following neoadjuvant chemoradiation were independently correlated with OS, with hazard ratio 2.04 (95% confidence interval [CI], 2.41-8.24), 6.63 (95% CI, 1.61-10.32), 9.21 (95% CI, 3.24-17.73) and 6.36 (95% CI, 3.27-11.34).
respectively. Similarly, multivariate analysis for disease free survival demonstrated that higher baseline NLR, dNLR along with advanced TNM stage at diagnosis, partial response with >10 residual tumor following neoadjuvant chemoradiation in addition to R1, R2 resections

| Characteristic          | No. of Patients and % | Overall survival of patients alive 38 months | Disease free survival of patients 34 free of disease | P value | P Value |
|-------------------------|------------------------|---------------------------------------------|-----------------------------------------------------|---------|---------|
| Age, years              |                        |                                             |                                                     |         |         |
| < 50                    | 38 (47.5%)             | 16 (42.1%)                                  | 14 (41.2%)                                          | 0.001*  | 0.002*  |
| ≥50                     | 42 (52.5%)             | 22 (57.9%)                                  | 20 (58.8%)                                          |         |         |
| Sex                     |                        |                                             |                                                     |         |         |
| Male                    | 56 (70%)               | 18 (47.4%)                                  | 19 (55.9%)                                          | 0.534   | 0.612   |
| Female                  | 24 (30%)               | 20 (52.6%)                                  | 15 (44.1%)                                          |         |         |
| Primary site            |                        |                                             |                                                     |         |         |
| Pylorus                 | 26 (32.5%)             | 3 (8%)                                      | 2 (6%)                                              | 0.645   | 0.731   |
| Cardia                  | 18 (22.5%)             | 15 (39.5%)                                  | 15 (44 %)                                           |         |         |
| Fundus                  | 16 (20%)               | 9 (23.6%)                                   | 8 (23.5%)                                           |         |         |
| Body                    | 12 (15%)               | 4 (10.5%)                                   | 2 (6%)                                              |         |         |
| Gastroesophageal Junction| 8 (10%)               | 7 (18.4%)                                   | 7 (20.5%)                                           |         |         |
Acute treatment-related toxicities

Details of acute chemoradiotherapy-induced toxicities by the Common Toxicity Criteria version 4.0 are listed in Table 6. Grade 4 toxicity was reported in 20% patients, and there were no treatment-related deaths. There were only four grade 3 late radiation toxicities observed (two esophagitis and one gastritis), as listed in Table 7.

Postoperative complications

Postoperative complications occurred in 34 patients (42.5%). The complications which were experienced within 30 days postoperatively were summarized in Table 8. The three most commonly encountered...
further ameliorate the treatment outcome of resectable gastric cancer, the postoperative chemoradiotherapy [5,8]. Consequently, in an attempt to in 50% of patients and only 40% 5-year survival can be expected after Nevertheless, R0 resection of the primary gastric cancer is achieved Discussion

Table 6: Selected chemotherapy and acute radiotherapy toxicities (n=80).

| Toxicity                       | Grade | 1 | 2 | 3 | 4 |
|--------------------------------|-------|---|---|---|---|
| Blood/bone marrow              |       |   |   |   |   |
| Hemoglobin decreased           |       | 36| 24| 4 | 2 |
| Neutropenia                    |       | 16| 6 | 16| 2 |
| Platelet count decreased       |       | 14| 6 | 8 | 4 |
| Gastrointestinal               |       |   |   |   |   |
| Anorexia                       |       |   |   |   |   |
| Dehydration                    |       | - | 10| 18| 0 |
| Esophagitis                    |       | - | 8 | 6 | 0 |
| Gastritis                      |       | - | 14| 2 | 0 |
| Nausea                         |       | - | 46| 14| 0 |
| Stomatitis                     |       | - | 8 | 12| 0 |
| Vomiting                       |       | - | 32| 8 | 4 |
| Febrile Neutropenia            |       | - | 6 | 4 | 1 |
| Neurology                      |       |   |   |   |   |
| Peripheral sensory neuropathy  |       | 12| 8 | 4 | 0 |
| Constitutional symptom         |       |   |   |   |   |
| Fatigue                        |       | 20| 30| 10| 0 |
| Weight decreased               |       | 12| 12| 14| 0 |

Table 7: Late radiation toxicities (n=80).

| Toxicity           | Grade | 1 | 2 | 3 | 4 |
|--------------------|-------|---|---|---|---|
| Gastrointestinal   |       |   |   |   |   |
| Esophagitis        |       | 1 | 2 | 3 | 0 |
| Gastritis          |       | 1 | 3 | 1 | 0 |
| Skin               |       | 2 | 0 | 0 | 0 |

complications were pneumonia, anastomosis fistula, and postoperative hemorrhage. Interventions were repeated in three patients (9.5%) and the average hospital stay was 12 days (range, 5–23).

Discussion

The primary treatment for early gastric cancer is surgery. Nevertheless, R0 resection of the primary gastric cancer is achieved in 50% of patients and only 40% 5-year survival can be expected after postoperative chemoradiotherapy [5,8]. Consequently, in an attempt to further ameliorate the treatment outcome of resectable gastric cancer, the feasibility and performance of preoperative chemoradiation was tested in several phase II trials [12,13,28]. In our study following the three-phase preoperative strategy using docetaxel-based chemoradiation, 85% of patients had an R0 resection. Additionally, a path CR was noted in 18 patients (22.5%), while a path PR in the form of less than 10% residual viable tumor was noted in 13 patients (16.2%). Our results are consistent with the results of Ajani et al. who reported that the three-phase preoperative strategy resulted in R0 resection, path CR, and path PR of 70%, 30%, and 24%, respectively [12]. Similarly, in the RTOG 9904 phase II trial of preoperative paclitaxel-based chemoradiation, the path CR and R0 resection rates were 26% and 77%, respectively [28]. Moreover, in another phase II trial conducted by Ajani et al. patients received two cycles of paclitaxel-based chemoradiation, and R0 resection was feasible in 78% of patients. A path CR rate of 20% and a path PR rate of 15% (<10% residual cancer cells in the resected specimen) were noted [13].

Over the past decades, emerging evidence confirmed the influence of inflammatory microenvironment on cancer. More understanding of the links between inflammation and cancer contributes to the prevention and treatment of tumor. Consequently, several biomarkers have been reported to reflect the link between inflammation and cancer, such as the systemic inflammatory biomarkers (NLR, dNLR, PLR, and LMR) which were considered as potential prognostic factors for different types of carcinoma in several studies [29-32]. Accordingly, the rationale of our study was to evaluate the impact of different clinico pathological prognostic indicators including baseline inflammatory response biomarkers (NLR, dNLR, PLR, and LMR) patient’s outcome.

The (ROC) demonstrated the ability of a baseline NLR, dNLR, LMR and PLR of 2.4, 1.7, 5.1 and 130 cut off values to predict DFS in surgically treated gastric cancer patients. Similarly, Deng et al. used ROC curves to devise the optimal cut-off levels of NLR, dNLR, PLR and LMR in predicting OS and DFS [33]. Patients were subsequently divided into two groups according to the optimal cut-off levels, with the high group ≥ the optimal cut-off levels and the low group that < the optimal cut-off levels. Our results demonstrated that patients with advanced stages, depth of invasion T3-T4, and lymph node N1-N3 had a higher NLR, dNLR, LMR and PLR than those with tumor stage I-II, depth of invasion T1-T2, and lymph node N0. Deng et al reported comparable association between advanced stage disease, T3-T4 depth of invasion, advanced nodal disease and elevated baseline biomarkers NLR, dNLR, LMR and PLR [33].

To the best of our knowledge, this retrospective study represents the first series that succeeded to find out cut off values of baseline biomarkers NLR, dNLR, LMR and PLR for gastric cancer patient receiving neoadjuvant chemoradiation prior to surgical resection. More importantly, our study demonstrated that baseline inflammatory response biomarkers NLR (P=0.001), d NLR (P=0.0024), LMR
(P=0.001) and PLR (P=0.003) were significantly associated with path CR and any pathologic response.

It is worth mentioning that our results indicated that NLR (≥ 2.4), dNLR (≥ 1.7), PLR (≥ 130), LMR (≥ 5.1), age of patients (≥ 50 years), depth of invasion T3, lymph node N1-N3, stage III, grade 3 tumors, R1 resection and partial response to preoperative chemoradiation course with >10% residual tumor were significantly associated with decreased OS, and DFS. However, on multiple regression analysis revealed that higher baseline NLR, dNLR along with advanced TNM stage at diagnosis and partial response with >10 residual tumor following neoadjuvant chemoradiation were independently correlated with poor OS and DFS.

Correspondingly, Deng et al. reported that in multivariate analysis, dNLR showed a significant association with OS, and NLR was closely associated with CSS and DFS [33]. The above results were supported by several mechanisms of inflammatory reaction to tumor. Elevated circulating neutrophils secrete pro-angiogenic factors, including vascular endothelial growth factor (VEGF). Circulating VEGF contributes to tumor angiogenesis and the progression of neoplasm [34,35]. VEGF was observed to be significantly overexpressed in gastric cancer tissue compared with normal tissue, and it has been verified that the overexpression of VEGF can induce cell proliferation and promoted cell cycle of GC cells by increasing the activation of VEGF receptor 2 in vitro [36,37]. It has been reported that neutrophil could inhibit T cell activation through the production of nitric oxide and arginase leading to depletion of lymphocyte mediated immune response. This can explain why increased NLR may act as an independently prognostic factor for CSS due to elevated neutrophil and relative lymphocytopenia [38,39].

In our study, postoperative complications occurred in 34 patients (42.5%). The three most commonly encountered complications within 30 days postoperatively were pneumonia, anastomosis fistula, and postoperative hemorrhage. Interventions were repeated in three patients (9.5%) and the average hospital stay was 12 days (range, 5-23). Similarly, Valenti et al. concluded from their analysis of the locally advanced gastric adenocarcinoma treated with preoperative chemoradiotherapy that general complications were the most commonly encountered, such as pneumonia and catheter-related infections [40].

The current study has several strengths

First: It is considered to be the first study to confirm the impact of different clinicopathological prognostic indicators including baseline inflammatory response biomarkers (NLR, dNLR, PLR, and LMR) on the outcome of gastric cancer patients treated with preoperative taxane based concurrent chemoradiation.

Second: There was homogeneity in the treatment used as all patients received neoadjuvant taxane based concurrent chemoradiation prior to surgical resection, which obviated the possible negative impact of different treatment modalities on clinical prognosis.

There are limitations to the current study

Firstly, the study was a retrospective design, with a small population size of 80 patients. Secondly, the peripheral blood findings were not compared to the findings of peritumoral inflammation in the primary tumor tissue. Consequently, further studies are needed to illuminate the relationship between inflammatory biomarkers and prognosis in patients with gastric cancer.

Conclusion

This study demonstrates that the baseline inflammatory response biomarkers NLR, dNLR, PLR and LMR showed a statistically significant association with different clinicopathological prognostic factors. In addition, NLR, dNLR may be considered as a potential independent prognostic indicator of clinical outcomes in gastric cancer patients receiving neoadjuvant chemoradiation. Ultimately perspective studies will be needed to further validate the prognostic potential of the baseline inflammatory response biomarkers in gastric cancer patients.

Conflict of Interest

All authors confirm that they did not receive any funds nor financial support from Faculty of Medicine, Alexandria University, Egypt or any other companies. Moreover, all authors affirm that there is no conflict of interest concerning this study.

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