Journal of
Cancer Science & Therapy

Zaghloul and Abbas, J Cancer Sci Ther 2017, 9:9
DOI: 10.4172/1948-5956.1000481

Research Article Open Access

The Role of Baseline Inflammatory Response Biomarkers in Predicting the Prognosis in Non Metastatic Gastric Cancer Patients Treated with Preoperative Chemoradiation

Hala Zaghloul[1]* and Ahmed Abbas[2]

[1]*Clinical Oncology Department Alexandria University, Egypt*
[2]*Surgical Oncology Department National Cancer Institute Cairo, Egypt*

Abstract

Purpose: To delve into the prospective of inflammatory-related indicators as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), derived neutrophil to lymphocyte ratio (dNLR), and lymphocyte to monocyte ratio (LMR) in forecasting the clinical outcome for gastric cancer managed with triple modality induction.

Methods: Participants were given two cycles of docetaxel, fluorouracil and cisplatin (TPF), succeeded by radiation (45 Gy) alongside concurrent fluorouracil plus taxotere, then finally surgical resection. The designated baseline prognosticators were linked with clinical-pathological factors. Their contribution to outcome were assessed using Log rank and Cox regression.

Results: The study's analysis revolved around 80 eligible participants. The triple modality induction ensued 22.5% complete response (PCR) alongside 47.5% and 42.5% 3-years estimated overall (OS) and disease-free survival (DFS), respectively. The receiver operator curves (ROC) cutoffs for baseline biomarker were registered at 2.4 (NLR), 1.7(dNLR), 5.1 (LMR) and 130 (PLR). Augmented prognosticators, stage III, R1 resection and >10 % residual tumor were substantially linked to worsened OS and DFS. Interestingly, the augmented dNLR and NLR were self-directed forecasters for deteriorating OS hazard ratio (HR) 2.04 (95% CI= 2.41-8.24), 6.63 (95% CI, 1.61-10.32) and DSF with (HR) 1.84 (95% CI= 3.27-7.36), 4.63 (95% CI= 3.61-12.12), respectively. None of the participants succumbed secondary to treatment toxicities although grade 4 side effects were attained by 20% of cases.

Conclusion: The triple modality induction in resectable gastric cancer is feasible with promising outcomes. The baseline inflammatory prognosticators attained a notable statistical link to many clinical/pathological variables. Moreover, NLR and dNLR behaved as autonomous indicators of clinical consequences for patients with gastric cancer managed with triple preoperative modality.

Keywords: Inflammatory response; Biomarkers in gastric cancer

Introduction

An amplified emphasis delved into improving abysmal outcomes for gastric cancer patients using perioperative chemotherapy with or without radiation [1-4]. At least three trials supported the survival benefits from postoperative chemo-radiotherapy [5-8]. The INT0116 study instituted postoperative chemo-radiotherapy as the supreme adjuvant approach. Further to this, a minimum of three trials have compared surgery with perioperative chemotherapy [9-11]. In the Seminal MAGIC trial, surgery was compared to surgery and perioperative chemotherapy [9]. Forty two percent of patients randomized to chemotherapy were able to accomplish the scheduled postoperative adjuvant course. Correspondingly, the substantial contenders for this approach was the intolerability of the postoperative chemotherapy, in addition to the comparatively elevated local recuurence [9-11]. The modest prognosis attained with the aforementioned approaches instigated the exploration of intensified triple modality preoperative strategy that entailed induction chemotherapy for two cycles to be succeeded by chemo-radiation course then surgery [12-14]. Fortunately, the preoperative strategy allowed for a surveillance window to explore the tumor biology prior to embarking on a major resection [12-14].

Furthermore, the assorted prospects for gastric cancer patients have mandated that effective biomarkers be adopted to optimize forecasting of outcomes. In recent work, chronic inflammation was extensively incriminated in the induction and promotion of carcinogenesis [15,16]. Malignant cells can modulate and optimize the performance of various leukocytes through T lymphocytes conditioning, this principle applies for neutrophils, monocytes and platelets alongside specified prostaglandins and chemokines [17,21]. Consequently, the priming of inflammatory cells can promote tumor evolution and the distant dissemination via the acceleration of inflammatory intermediaries and cytokines [22]. Lately, many forecasters driven from 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 (LMR) have been extensively explored as prognosticators in various cancers [23-27]. In reality, only 1 or 2 biomarkers have been explored in gastric cancer patients [11,17-21]. In addition, the heterogeneity in the threshold values for the previously tested indicators doubted their sensitivities and specificities in gastric

***Corresponding author:** Dr. Hala Zaghloul, Department of Clinical Oncology, Faculty of Medicine, Alexandria University, Egypt, Tel: 00201223926059; Fax: 002034290746; E-mail: h_zagloul@yahoo.com

Received July 25, 2017; **Accepted** September 04, 2017; **Published** September 08, 2017

Citation: Zaghloul H, Abbas A (2017) The Role of Baseline Inflammatory Response Biomarkers in Predicting the Prognosis in No Metastatic Gastric Cancer Patients Treated with Preoperative Chemoradiation. Cancer Sci Ther 9: 608-616. doi: 10.4172/1948-5956.1000481

cancer patients. As a result, further assessment of these prognosticators became imperative. Concordantly, we focused on analyzing baseline NLR, d NLR, LMR and PLR as prognosticators that may predict the outcome for gastric cancer managed with triple modality strategy.

Materials and Methods

A retrospective review of gastric cancer patients treated at Surgical Oncology department National Cancer Institute Cairo University and Clinical Oncology department Alexanderia University, starting from January 2013 till December 2016 following Institutional Board approval (IRB). The participating patients provided their consent through signed forms. The patient's records were studied to segregate patients who received triple modality induction to collect the required clinical/pathological characteristics. The calculation of tested pretreatment prognosticators NLR, dNLR = neutrophil count to (white cell count-neutrophil count), PLR and LMR were carried out.

Criteria for inclusion

Non metastatic, localized, histologically verified T1, N1–2, and T2–3, N0–3 gastric or gastroesophageal adenocarcinoma. All participants should have tolerated two induction chemotherapy cycles that had fluorouracil 750 mg/m2/day on days1to5 cisplatin 20mg/m2/day on days1to5 and docetaxel 75 mg/m2.Four weeks later a dose of 45 Gy over five weeks was offered to patients with daily doses of 300 mg/m2 fluorouracil via continuous infusion in addition to weekly 20 mg/m2 docetaxel . R0 or R1 resections were exclusively added to the study. The R0 resection entailed radical elimination of clinical disease with the closest acceptable safety boundary of 2mm width. While R1 resections involved microscopic residual carcinomas left in the tumor bed. The eligible participants were offered either subtotal or total gastrectomy based on the origins of their disease. The ideal lymph node dissection aimed at retrieving at least 15 regional lymph nodes. On the contrary, participants who harbored or developed distant dissemination in the triple modality phase and those who suffered macroscopic remaining carcinomas following surgery were excluded from the studied population.

Statistical Consideration

The interaction between the verified prognosticators and various clinical/pathological variables on was carried by the Mann-Whitney U test (between 2 groups) or Kruskal- Wallis test (≥3 groups). The receiver operator curves (ROC) were deployed to discover the possible cutoffs of tested prognosticators. An area under the curve (AUC) < 0.5 demonstrates a non-informative test. The Kaplan-Meier alongside Cox regression and log rank approaches were applied for the survival analysis. The SPSS 16.0 package program was employed to carry out all statistical work.

Results

The inclusion requisites were fulfilled in 80 patients. The sample consisted of 24 female patients, registering at 30% of the pool, while 56 or 70% were males. The median age stood at 51 years. The baseline median values for the prognosticators were registered at 3.12 (NLR), 2.31 (dNLR), 3,97 (LMR) and 139 (PLR). The characteristics of all studied participants are illustrated in [Table1].

The implemented ROC had a baseline dNLR of 1.7 and NLR of 2.4, cutoff for forecasing DFS (AUC at 0.703&0.683 at 75.7%, 72% sensitivity and a 80% and 78% specificity), respectively (Figure 1). Moreover, it showed the ability of baseline PLR and LMR to forecast DFS (AUC stood at 0.695&0.585 at 71.2%, 68.2% sensitivity and 69.1%, 60.2% specificity), respectively. Moreover, the optimum LMR (5.1) and PLR (130) cutoffs were also established. Patients were split into two categories as per the threshold levels identified.

The verified prognosticators displayed a considerable link to initial disease burden as amplified baseline (PLR, LMR, dNLR and NLR) were principally encountered in poorly differentiated primaries alongside stage III disease which comprised larger tumors and extensive nodal diseases as illustrated in (Table 2). Precisely 85% of the participants, had complete resection. Another 15% or 12 patients had R1 resection. Both primary tumors and the draining lymph nodes attained total resolution of malignant cells as verified pathologically (path CR) in 22.5% of the patients i.e. 18 individuals. While 16.2% i.e. 13 patients developed relatively advantageous pathological partial response (path PR) as less than 10% malignant cells were verified. Another 23 patients, who accounted for 28.7% of the sample, attained path PR with greater remaining cancer burden mounting up to 10-50% residual viable disease identified in postoperative pathology. The rate was different for 12 patients or 15% of the sample that presented with more than 50% residual disease. Overall, the pathologic response rate stood at 82.5%. The 14 patients that remained experienced steady or advanced disease subsequent to neoadjuvant course. Subsequent to gastrectomy, primary carcinomas in 23 or 28.7% of cases was T3, while 16 patients or 20% were T2, 21 patients or 26.3% presented T1, and finally 20 patients or 25% presented T0. N0 cancer was observed in 27 patients or 33.8% of the pool, while N1 was observed in 41 patients or 51.2%, and N2 was observed in 15% or 12 patients (Table 3). The median for the nodes stood at 19, with a range of 6 to 32. "The median for nodes with carcinoma stood at 4 while the median for cancer-free stood at 15. It is worth stating that accentuated pathologic response was considerably related to lesser primary tumor and nodal burdens (P=0.003), (P=0.002) alongside reduced expressions of NLR (P= 0.001) , d NLR(P= 0.0024), LMR (P=0.001) and PLR(P=0.003), respectively (Table 4) (Figures 2 and 3)."

During the surveillance around 57.5% of the patients, or 46 people, failed treatment either locally or systemically. From this, 52.5% or 42 succumbed secondary to their cancer. The estimated OS and DFS mounted to 47.5% and 42.5% with a median time interval that pointed to 25 and 20 months, in that order. The worst survivals were experienced by patients with extensive remaining cancer wider than 10% (Figure 4) alongside those who expressed enhanced NLR (≥2.4) (Figures 5 and 6), dNLR (≥1.7) (Figures 7 and 8), PLR (≥130) and LMR (≥ 5.1) (Table 5). Furthermore, the amplified baseline NLR and dNLR alongside greater remaining tumor burden > 10% were substantially linked with dismal OS, with hazard ratio 2.04 (95% confidence interval [CI], 2.41-8.24), 6.63 (95% CI, 1.61-10.32) and 6.36 (95% CI, 3.27-11.34). Concordantly, worsened DFS was attributed to augmented baseline NLR, dNLR and >10% residual tumor with hazard ratio 1.84 (95% confidence interval [CI], 3.27-7.36), 4.63 (95% CI, 3.61-12.12), and 7.35 (95% CI, 2.57-13.54).

More information on toxicities that result from acute chemo-radiotherapy were summarized in (Table 6). None of the participants succumbed secondary to treatment toxicities although grade 4 side effects were attained by 20% of them. Detailed delayed radiation toxicities were reported in (Table 7)."

Postoperative complications

Such issues presented in 42.5% of the patients, i.e. 34 individuals. The issues manifested within 30-day period after the surgery were listed in [Table8]. Anastomosis fistula, pneumonia, and hemorrhage after the

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%
T stage		
T1	16	20%
T2	20	25%
T3	44	55%
N stage		
N0	18	22.50%
N1	48	60%
N2	14	17.50%
Stage group		
IIA	32	40%
IIB	40	50%
IIIA	8	10%
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	139	--
<130	33	41.30%
≥ 130	47	58.70%

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

operation were the most common problems. Three patients, or 9.5% of the sample, were given interventions, while the median for the hospital stay stood at 12 days, within a five to 23-day range.

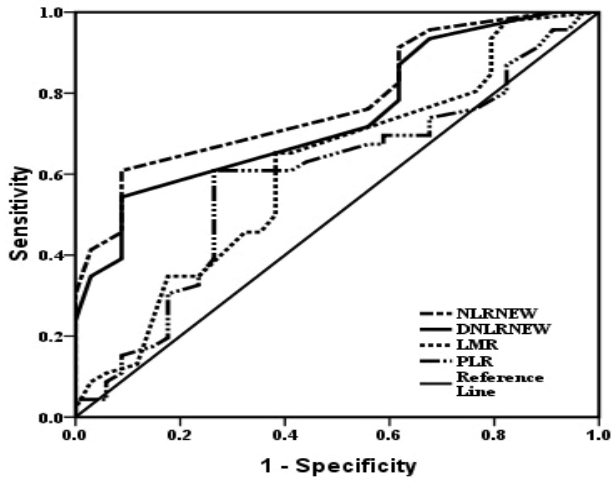

Figure 1: Optimal cut-off levels for NLR, dNLR, PLR and LMR were applied with ROC curves for cancer -specific survival.

Discussion

Several phase II trials were conducted to test the efficacy of preoperative chemo-radiation in improving abysmal outcomes previously attained in gastric cancer [12,13,28]. Eighty five percent of participants experienced R0 resection after a triple preoperative docetaxel-based modality. Furthermore, a CR path was noted in 22.5% or 18 of the participants. Ajani et al. concluded that applying the triple preoperative modality induced R0 resection and PCR in 70% and 30 % of the cases, correspondingly [12]. Concordantly, the RTOG 9904 trial concluded that PCR and R0 resection were accomplished by 26 and 77 % of similarly managed cases [28].

Recently, innovative researches have corroborated that cancer is influenced by inflammatory cells interaction in tumor microenvironment. An explicit interpretation of the contribution of individual cell in the inflammatory cascade induced by tumorigenesis will pave the pathway to attain precise targeted cancer therapy alongside the deceleration or even abolishment of carcinogenesis [29-32]. Consequently, our wok perspectives had revolved around shading lighter on the interaction of the specified prognosticators with conventional clinical/pathological elements, as well as their modulation of the studied patient outcomes. The ROC established baseline cut off values i.e. NLR (2. 4), dNLR (1.75), LMR (5. 1) and PLR (130) as forecasters of DFS in the studied participants. Deng et al conquered with our inference that augmented expressions of NLR, dNLR , LMR and PLR were linked to greater tumor burdens[33]."

It can be acknowledged that it is primary study to efficaciously establish the optimal cutoff values for baseline verified prognosticators in gastric cancers managed with triple preoperative modality. The worst survivals were experienced by patients with extensive remaining cancer >10% alongside those who expressed enhanced NLR (≥2.4) , dNLR (≥1.7)) , PLR (≥130) and LMR (≥ 5.1).Concordantly, Deng et al ensued a substantial link of dNLR , NLR to survival consequences[33].

The outcomes emphasized in our work are sustained by the innovative body of evidence elaborating the chain of pathways stimulated by inflammatory cells in carcinogenesis [34-39].For instance enhanced neutrophils produce angiogenesis promoting factors, such as vascular endothelial growth factor (VEGF) which enhances neoplasm

Characteristic	No. of patients	%	Baseline NLR	Baseline dNLR		Baseline LMR		Baseline PLR	
			P value	Median	P value	Median	P value	Median	P value
Age, years									
<50	38	47.50%	0.646	1.9	0.478	3.6	0.347	125	0.673
≥ 50	42	52.50%	-	1.8	-	3.9	-	128	
Sex									
Male	56	70%	0.684	1.9	0. 473	3.1	0.521	122	0.0164*
Female	24	30%	-	1.7	-	3.4	-	125	
Primary site									
Pylorus	26	32.50%	-	1.7	-	2.7	-	121	0.348
Cardia	18	22.50%	0.783	1.9	0.623	3.6	0.546	123	
Fundus	16	20%	-	2.1	-	3.8	-	118	
Body	12	15%	-	1.6	-	4.6	-	125	
Gastroesophageal junction	8	10%	-	2.3	-	4.3	-	122	
Histopathological type									
Papillary	4	5%	-	1.6	-	3.2	-	126	0.0236*
Tubular	17	21.20%	0.0412*	1.9	0.0342*	3.6	0.0321*	128	
Poorly differentiated	40	50%	-	3.1	-	5.1	-	139	
Mucinous	12	15%	-	3.7	-	4.9	-	141	
Signet ring	7	8.80%	-	3.8	-	5.2	-	145	
Tumor grade									
G1	2	2.50%	0.0112*	1.6	0.0214*	2.5	0.0345*	110	0.0215*
G2	28	35%	-	1.9	-	3.1	-	121	
G3	50	62.50%	-	4.2	-	5.3	-	156	
T stage									
T1	16	20%	-	1.6	-	3.1	-	123	0.0126*
T2	20	25%	0.0216*	2.1	0.0315*	3.4	0.0316*	137	
T3	44	55%	-	4.1	-	5.3	-	141	
N stage									
N0	18	22.50%	-	1.5	-	2.9	-	122	0.0112*
N1	48	60%	0.0234*	2.3	0.0156*	3.9	0.0134*	138	
N2	14	17.50%	-	4.3	-	5.6	-	149	
Stage group									
IIA	32	40%	-	1.9	-	3.1	-	134	0.011*
IIB	40	50%	0.0245*	2.8	0.0321*	4.7	0.034*	142	
IIIA	8	10%	-	5.3	-	5.9	-	150	

Table 2: Association between inflammatory biomarkers and different clinicopathological parameters.

Variables	Baseline		After induction chemoradiation		Wilcoxon signed rank test Asymp. sig (2 tailed)
	No of pts	%	No of pts	%	
T stage					
T0	0	-	20	25%	0.002*
T1	0	-	21	26.30%	
T2	20	25%	16	20%	
T3	60	75%	23	28.70%	
N stage					
N0	18	22.5%	27	33.80%	0.034*
N1	49	61.2%	41	51.20%	
N2	13	16.3%	12	15%	

Table 3: Patient Response to Chemoradiotherapy (N=80).

evolution [34,35].Correspondingly , accentuated expression of VEGF was appreciated in gastric cancer specimens compared to normal gastric tissues and it was linked to augmented stimulation of VEGF receptor 2 that induced proliferation gastric cancer cells [36,37]. Surprisingly, studies clarified that neutrophils suppress T cell function through release of cytotoxic chemokines (nitric oxide and arginase) resulting in abolishment of lymphocyte mediated tumoricidal pathways. Consequently, augmented NLR behaved as a self-regulating indicator for cancer specific survival for certain cancers [38,39]."

Our study delved into the interaction of innovative prognosticators (NLR, dNLR , PLR , LMR) with different clinical/pathological indicators and scrutinized on their prospective in forecasting gastric cancer patients' outcome, specifically those that have been given preoperative triple modality. Additional, the studied participants received consistent neoadjuvant treatment which precluded any confounding influence on prognosis that might be induced by applying dissimilar treatment modalities.

However, the conducted work suffered certain restrictions caused by its retrospective strategy alongside the limited number of participants eligible for inclusion. Additionally, we did not explore

Characteristic	Patients	No	%CR	P
Age, years				
Median	51	-	-	-
Range	39-69	-	-	-
Sex				
Male	56	12	21.40%	0.74
Female	24	6	25%	
Primary site				
Pylorus	26	6	23.10%	0.78
Cardia	18	4	22.20%	
Fundus	16	3	18.70%	
Body	12	3	25%	
Gastroesophageal Junction	8	2	25%	
Histopathological type				
Papillary	4	2	50%	0.04*
Tubular	17	6	35.30%	
Poorly differentiated	40	10	25%	
Mucinous	12	0	0%	
Signet Ring	7	0	0%	
Tumor grade				
G1	2	2	100%	0.03*
G2	28	6	21.40%	
G3	50	10	20%	
T stage				
T1	5	5	100%	0.003*
T2	20	12	60%	
T3	55	1	0.02%	
N stage				
N0	18	12	67%	0.002*
N1	49	6	33%	
N2	13	0	-	
Stage group				
IIA	32	14	78%	0.003*
IIB	40	4	22%	
IIIA	8	0	-	
Inflammatory response biomarkers				
NLR				
Median	3.12	-	-	0.001*
<2.4	27	12	67%	
≥ 2.4	53	6	33%	
dNLR				
Median	2.31	-	-	0.0024*
<1.7	32	14	78%	
≥ 1.7	48	4	22%	
LMR				
Median	3.97	-	-	0.001*
<5.1	49	13	72%	
≥ 5.1	31	5	28%	
PLR				
Median	139	-	-	0.003*
<130	33	11	61%	
≥ 130	47	7	39%	

Table 4: Association between pathological complete response and different clinicopathological parameters.

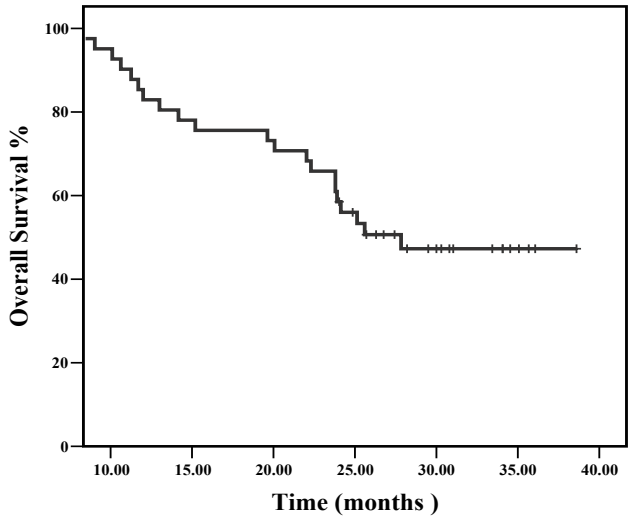

Figure 2: Overall survival in months.

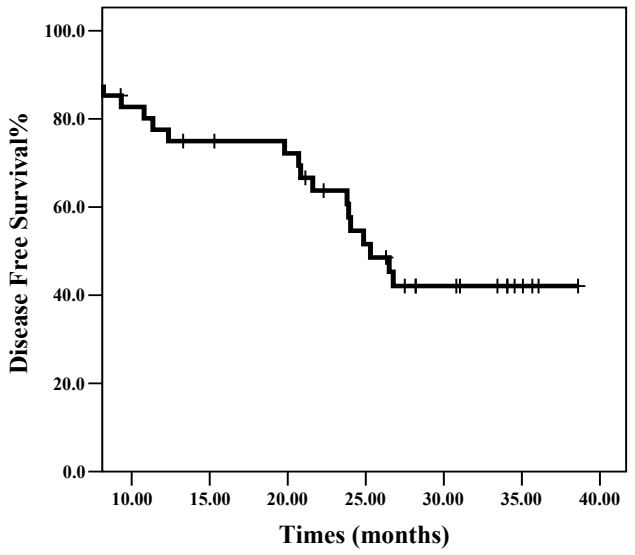

Figure 3: Disease free survival in months.

the modulation of the tested prognosticators can exert on tumor infiltrating lymphocytes.

Conclusion

The triple modality induction in resectable gastric cancer is feasible with promising outcomes. The baseline inflammatory prognosticators attained a notable statistical link to many clinical/pathological variables. Moreover, NLR and dNLR were revealed as independent prognosticators gastric cancer managed with triple preoperative modality. Finally, future work is required to validate their prognostic potential.

Conflict of Interest

The authors confirm that no form of financial support, including funding, was received for the study. They further confirm that the study at hand presented no struggle of interest.

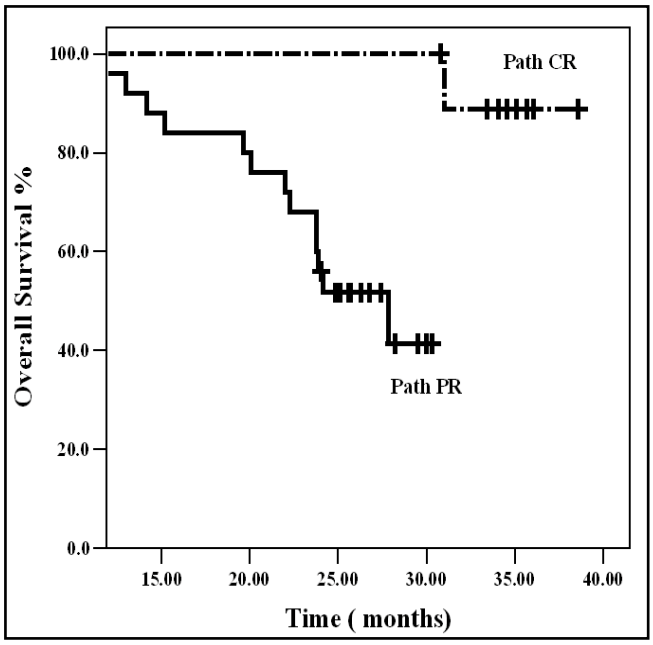

Figure 4: Overall survival by pathological response.

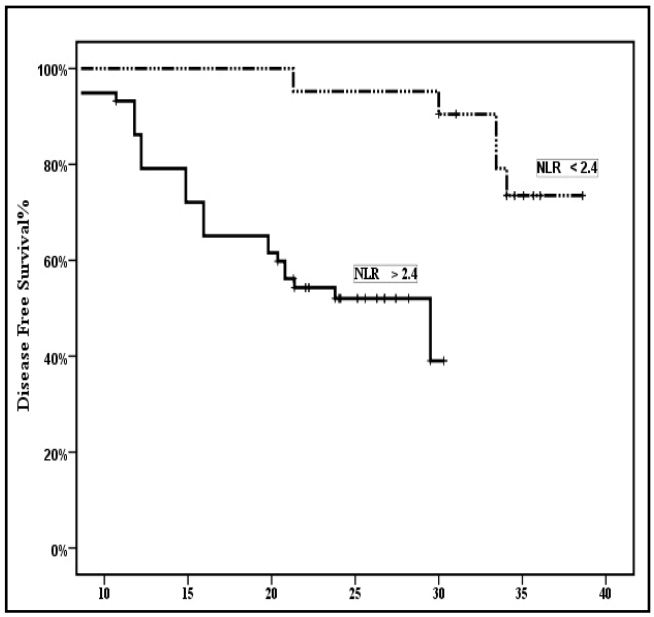

Figure 6: Disease free survival in months.

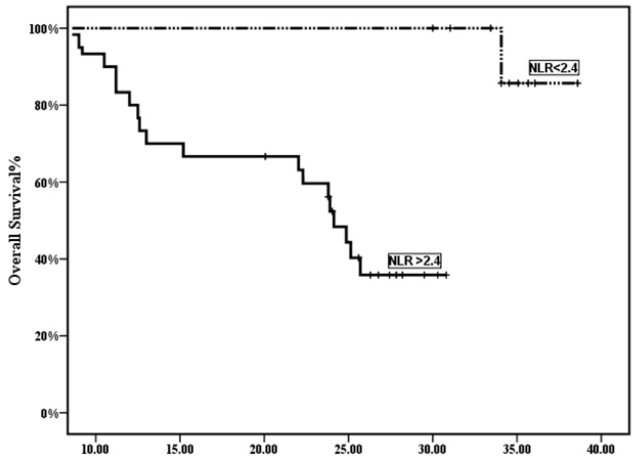

Figure 5: Overall survival in months.

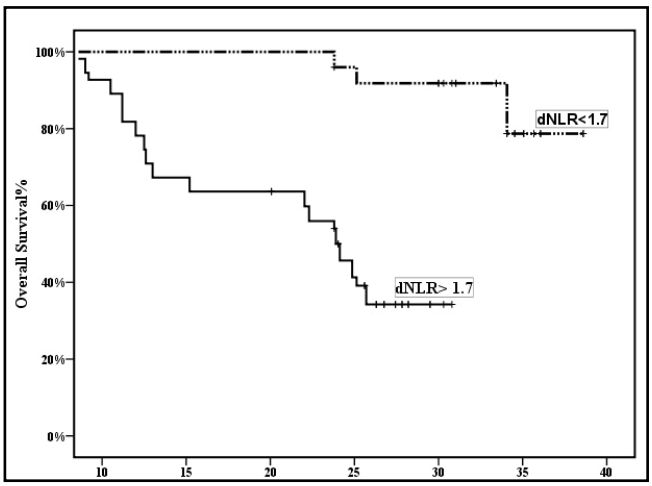

Figure 7: Overall survival in months.

Characteristic	No. of Patients and %	Overall survival of patients alive 38		Disease free survival of patients 34 free of disease	
		no (%)	P value	no (%)	P Value
Age, years					
< 50	38 (47.5%)	16 (42.1%)	0.001*	14 (41.2%)	0.002*
≥50	42 (52.5%)	22 (57.9%)		20 (58.8%)	
Sex					
Male	56 (70%)	18 (47.4%)	0.534	19 (55.9%)	0.612
Female	24 (30%)	20 (52.6%)		15 (44.1%)	
Primary site					
Pylorus	26 (32.5%)	3 (8%)	0.645	2 (6%)	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%)	

Histopathological type at diagnosis					
Papillary	4 (5%)	4 (10.5%)	0.145	4 (12%)	0.632
Tubular	17 (21.2%)	16 (42.1%)		16 (47%)	
Poorly differentiated	40 (50%)	15 (39.4%)		13 (38 %)	
Mucinous	12 (15%)	3 (8%)		1 (3%)	
Signet Ring	7 (8.8%)	0		0	
Tumor Grade at diagnosis					
G1	2 (2.5%)	2 (5%)	0.001*	2 (6%)	0.011*
G2	28 (35%)	28 (74%)		28 (82%)	
G3	50 (62.5%)	8 (21%)			
T stage at diagnosis					
T1	16 (20%)	16 (42%)	0.013*	16 (47%)	0.002*
T2	20 (25%)	19 (50%)		17 (50%)	
T3	44 (55%)	3 (8%)		1 (3%)	
N stage at diagnosis					
N0	18 (22.5%)	18 (47.4%)	0.002*	18 (53%)	0.031*
N1	48 (60%)	16 (42.1%)		14 (41%)	
N2	14 (17.5%)	4 (10.5%)		2 (6%)	
Stage group at diagnosis					
IIA	32	29 (76.3%)	0.001*	26 (76%)	0.004*
IIB	40	9 (23.7%)		8 (24%)	
IIIA	8	0		0	
Pathological response					
Complete response at primary site and LN	18 (22.5%)	18 (47.4%)	0. 001*	18 (53%)	0.003*
Partial response with <10% residual tumor	13 (16.2%)	12 (31.6%)		12 (35%)	
Partial response with 10% to 50% residual tumor	23 (28.8%)	8 (21%)		4 (12%)	
Partial response with >50% residual tumor	12 (15%)	0		0	
Stable or progressive disease	14 (17.5%)	0		0	
Type of resection					
R0	68 (85%)	30 (79%)	0.004*	28 (74%)	0.002*
R1	12 (15%)	8 (21%)		6 (16%)	
Inflammatory Response biomarkers at diagnosis					
NLR					
Median	3.12		0.013*		0.032*
< 2.4	27 (33.8%)	24 (63.2%)		22 (65%)	
≥ 2.4	53 (66.2%)	14 (36.8%)		12 (35%)	
dNLR					
Median	2.31	-	0.016*	-	0.011*
< 1.7	32 (40%)	25 (65.8%)		23 (68%)	
≥ 1.7	48 (60%)	13 (34.2%)		11 (32%)	
LMR					
Median	3.97		0. 014*	-	0. 021*
< 5.1	49 (61.2%)	28 (73.7%)		26 (76.5%)	
≥ 5.1	31 (38.8%)	10 (26.3%)		8 (23.5%)	
PLR					
Median	139	-	0.027*	-	0.001*
< 130	33 (41.3%)	26 (68.4%)		25 (73.5%)	
≥ 130	47 (58.7%)	12 (31.6%)		9 (26.5%)	

Table 5: Association between different clinicopathological parameters and clinical prognosis.

References

1. Jemal A, Bray F, Center MM, Ferly J, Ward E, et al. (2011) Global cancer statistics. CA Cancer J Clin 61: 69-90.
2. Siegel R, Ward E, Brawley O, Jemal A (2011) Cancer statistics, 2011: The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 61: 212-236.
3. Agboola O (1994) Adjuvant treatment in gastric cancer. Cancer Treat Rev 20: 217-240.
4. Gunderson LL, Sosin H (1982) Adenocarcinoma of the stomach: Areas of failure in a re-operation series (second or symptomatic look) clinicopathologic correlation and implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 8: 1-11.
5. Macdonald JS, Smalley SR, Benedetti J, Hundhal SA, Estes NC, et al. (2001) Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 345: 725-730.
6. Dent DM, Werner ID, Novis B, Cheverton P, Brice P (1979) Prospective randomized trial of combined oncological therapy for gastric carcinoma. Cancer 44: 385-391.

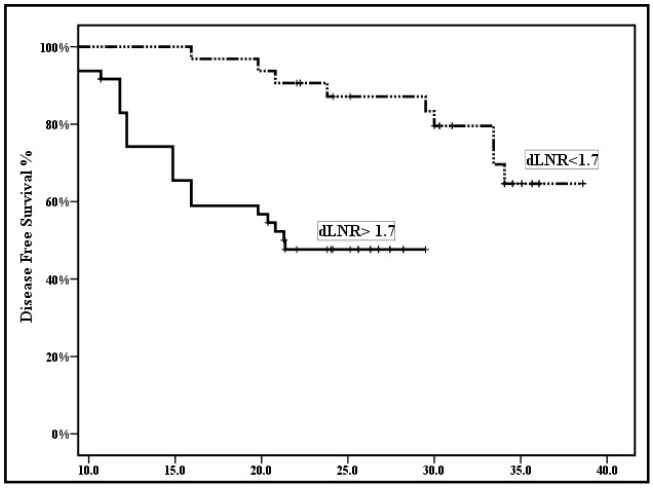

Figure 8: Disease free survival in months.

Toxicity	Grade			
	1	2	3	4
Blood/bone marrow				
Hemoglobindecreased	36	24	4	2
Neutropenia	16	6	16	2
Platelet count decreased	14	6	8	4
Gastrointestinal				
Anorexia	-	26	8	3
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 6: Selected chemotherapy and acute radiotherapy 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

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

Complications	No. of Patients (80)	%
No. of patients with complications	34	42.5
Wound infection	6	7.5
Anastomosis fistula	4	5
Intra-abdominal abscess	6	7.5
Postoperative haemorrhage	5	6.3
General complications		
Catheter sepsis	4	5
Thromboembolism	4	5
Pneumonia	5	6.2

Table 8: Surgical morbidity and mortality.

7. Moertel CG, Childs DS, O'Fallon JR, Holbrook MA, Schutt AJ, et al. (1984) Combined 5-fluorouracil and radiation therapy as a surgical adjuvant for poor prognosis gastric carcinoma. J Clin Oncol 2: 1249-1254.

8. Schwartz GK, Winter K, Minsky BD, Crane C, Thomson PJ, et al. (2009) Randomized phase II trial evaluating two paclitaxel and cisplatin-containing chemoradiation regimens as adjuvant therapy in resected gastric cancer (RTOG-0114). J Clin Oncol 27: 1956-1962.

9. Songun I, Keizer HJ, Hermans J, Klementschitsch P, De Vries JE, et al. (1999) Chemotherapy for operable gastric cancer: Results of the Dutch randomised FAMTX trial. The Dutch Gastric Cancer Group (DGCG). Eur J Cancer 35: 558-562.

10. Boige V, Pignon J, Saint-Aubert B, Lasser P, Conroy T (2007) Final results of a randomized trial comparing preoperative 5-fluorouracil/cisplatin to surgery alone in adenocarcinoma of stomach and lower esophagus (ASLE): FNLCC ACCORD07-FFCD 9703 trial (abstract). J Clin Oncol 25: 4510.

11. Ajani JA, Mansfield PF, Lynch PM, Pisters PW, Feig B, et al. (1999) Enhanced staging and all chemotherapy preoperatively in patients with potentially resectable gastric carcinoma. J Clin Oncol 17: 2403-2411.

12. Ajani JA, Mansfield P, Janjan N, Morris J, Pisters PW, et al. (2004) Multi-institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma. J Clin Oncol 22: 2774-2780.

13. Ajani JA, Mansfield PF, Crane CH, WuTT, Lunagomez S, et al. (2005) Paclitaxel-based chemoradiotherapy in localized gastric carcinoma: degree of pathologic response and not clinical parameters dictated patient outcome. J Clin Oncol 23: 1237-1244.

14. Ajani JA, Fodor MB, Tjulandin SA, Moiseyenko VM, Chao Y, et al. (2005) Phase II multi institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. J Clin Oncol 23: 5660-5667.

15. Mantovani A, Allavena P, Sica A, Balkwill F (2008) Cancer-related inflammation. Nature 454: 436-444.

16. Lee K, Hwang H, Nam KT (2014) Immune response and the tumor microenvironment: How they communicate to regulate gastric cancer. Gut Liver 8: 131-139.

17. Mantovani A, Allavena P, Sica A, Balkwill F (2008) Cancer-related inflammation. Nature 454: 436-444.

18. Stoppacciaro A, Melani C, Parenza M, Mastracchio A, Bassi C, et al. (1993) Regression of an established tumor genetically modified to release granulocytecolony-stimulating factor requires granulocyte-T cell cooperation and T cell-produced interferon gamma. J Exp Med 178: 151-161.

19. Bellocq A, Antoine M, Flahault A, Philippe C, Crestani B, et al. (1998) Neutrophil alveolitis in bronchioloalveolar carcinoma: Induction by tumor-derived interleukin-8 and relation to clinical outcome. Am J Pathol 152: 83-92.

20. De Larco JE, Wuertz BR, Furcht LT (2004) The potential role of neutrophils in promoting the metastatic phenotype of tumors releasing interleukin-8. Clin Cancer Res 10: 4895-4900.

21. Ghasemzadeh M, Hosseini E (2013) Platelet-leukocyte crosstalk: Linking proinflammatory responses to procoagulant state. Thromb Res 131: 191-197.

22. Balkwill F, Mantovani A (2001) Inflammation and cancer: Back to Virchow? Lancet 357: 539-545.

23. Cho IR, Park JC, Park CH, Jo JH, Lee HJ, et al. (2014) Pre-treatment neutrophil to lymphocyte ratio as a prognostic marker to predict chemotherapeutic response and survival outcomes in metastatic advanced gastric cancer. Gastric Cancer 17: 703-710.

24. Halazun KJ, Aldoori A, Malik HZ, Al-Mukhtar A, Prasad KR, et al. (2008) Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases. Eur J Surg Oncol 34: 55-60.

25. Oh BS, Jang JW, Kwon JH, You CR, Chung KW, et al. (2013) Prognostic value of C-reactive protein and neutrophil-to-lymphocyte ratio in patients with hepatocellular carcinoma. BMC Cancer 13: 78.

26. Hirashima M, Higuchi S, Sakamoto K, Nishiyama T, Okada H (1998) The ratio of neutrophils to lymphocytes and the phenotypes of neutrophils in patients with early gastric cancer. J Cancer Res Clin Oncol 124: 329-334.

27. Yamanaka T, Matsumoto S, Teramukai S, Ishiwata R, Nagai Y, et al. (2007) The baseline ratio of neutrophils to lymphocytes is associated with patient prognosis in advanced gastric cancer. Oncology 73: 215-220.

28. Ajani JA, Winter K, Okawara GS, Donohue JH, Peter W, et al. (2006) Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): Quality of combined modality therapy and pathologic response. J Clin Oncol 24: 3953-3958.

29. Proctor MJ, McMillan DC, Morrison DS, Fletcher CD, Horgan PG, et al. (2012) A derived neutrophil to lymphocyte ratio predicts survival in patients with cancer. Br J Cancer 107: 695-699.

30. Crumley AB, McMillan DC, McKernan M, McDonald AC, Stuart RC (2006) Evaluation of an inflammation-based prognostic score in patients with inoperable gastro-oesophageal cancer. Br J Cancer 94: 637-641.

31. Satomi A, Murakami S, Ishida K, Mastuki M, Hashimoto T, et al. (1995) Significance of increased neutrophils in patients with advanced colorectal cancer. Acta Oncol 34: 69-73.

32. Kemal Y, Yucel I, Ekiz K, Demirag G, Yilmaz B, et al. (2014) Elevated serum neutrophil to lymphocyte and platelet to lymphocyte ratios could be useful in lung cancer diagnosis. Asian Pac J Cancer Prev 15: 2651-2654.

33. Deng Q, He B, Liu X, Yue J, Ying H, et al. (2015) Prognostic value of pre-operative inflammatory response biomarkers in gastric cancer patients and the construction of a predictive model. J Transl Med 13: 66.

34. Kusumanto YH, Dam WA, Hospers GA, Meijer C, Mulder NH (2003) Platelets and granulocytes, in particular the neutrophils, form important compartments for circulating vascular endothelial growth factor. Angiogenesis 6: 283-287.

35. Shamamian P, Schwartz JD, Pocock BJ, Monea S, Whiting D, et al. (2001) Activation of progelatinase A (MMP-2) by neutrophil elastase, cathepsin G, and proteinase-3: A role for inflammatory cells in tumor invasion and angiogenesis. J Cell Physiol 189: 197-206.

36. Li L, Wang L, Song P, Geng X, Liang X, et al. (2014) Critical role of histone demethylase RBP2 in human gastric cancer angiogenesis. Mol Cancer 13: 81.

37. Zhang J, Wang P, Zhu J, Wang W, Yin J, et al. (2014) SPARC expression is negatively correlated with clinicopathological factors of gastric cancer and inhibits malignancy of gastric cancer cells. Oncol Rep 31: 2312-2320.

38. Muller I, Munder M, Kropf P, Hansch GM (2009) Polymorphonuclear neutrophils and T lymphocytes: Strange bedfellows or brothers in arms? Trends Immunol 30: 522-530.

39. Ohtani H (2007) Focus on TILs: Prognostic significance of tumor infiltrating lymphocytes in human colorectal cancer. Cancer Immun 7: 4.

40. Valenti V, Hernaandez-Lizoain JL, Martinez Requeira F, Gil A, Marti P, et al. (2009) Analysis of postoperative morbidity in patients with gastric adenocarcinoma treated using a protocol of preoperative chemoradiotherapy and surgery. Cir Esp 86: 351-357.