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ORIGINAL ARTICLE

Dynamic perspective of the neutrophil-to-lymphocyte ratio in metastatic gastric cancer

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Summary

Purpose: *The neutrophil-to-lymphocyte ratio (NLR) is an accessible marker from a routine blood test. This study explored the prognostic and predictive value of a change in NLR (c-NLR) after chemotherapy, baseline NLR (bNLR) and chemotherapy response, in metastatic gastric cancer (mGC) patients.*

Methods: *A total of 116 mGC patients treated between 2009 to 2019 at seven hospitals from Galician Research Group on Digestive Tumors (GITuD) were reviewed in a multicentre, ambispective and observational study. NLR was calculated and the optimal cut-off was defined as NLR=3.96 based on ROC method. NLR was determined at baseline and after two chemotherapy cycles in first line treatment. Change NLR was calculated as NLR after two chemotherapy cycles minus bNLR. The relation of bNLR and c-NLR to overall survival (OS) was evaluated by Kaplan-Meier method and compared by log-rank test. Dynamic Score (DScore) based on c-NLR and baseline NLR were correlated with OS and radiological response. Univariate, multivariate and chi-square analyses were performed.*

Results: *Median patient age was 68.7 years, and 66% were male. Univariate analysis showed OS correlation for bNLR ≥3.96 (5.97 vs 10.87 months, p=0.001), c-NLR increase (6.63 vs 10.34 months, p=0.021) and DScore (12.74 vs 7.68 vs 2.43 months, p<0.001). High DScore was associated with radiological progression after two cycles (x^2=10.26, p=0.006). Multivariate analysis: bNLR ≥3.96 (HR=2.16, p=0.003) and c-NLR increase (HR= 2.36, p=0.003) were prognostic factors of poor OS.*

Conclusion: *High bNLR and increased NLR after chemotherapy were associated with worse outcome. Dynamic measurement of NLR provides information for stratifying patients to guide optimal treatment.*

Key words: *metastatic gastric cancer, NLR, change NLR, prognostic value, lymphocyte ratio, Dynamic Score*

Introduction

Gastric cancer is a heterogeneous disease associated with poor survival in the metastatic setting, with one-year overall survival (OS) rate of approximately 5%. In recent years, a multidisciplinary approach has emerged, while new drugs have also been approved, which will hopefully

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show improved outcomes over time. In 2010, the ToGA trial [1] was the first targeted therapy trial in gastric cancer to show a survival benefit, with an improvement of 2.7 months in OS in HER2-positive patients with advanced disease treated with trastuzumab plus chemotherapy. Subsequently, anti-VEGF therapy with ramucirumab associated to paclitaxel also demonstrated a survival benefit in second-line treatment in the RAINBOW trial [2], and in monotherapy in patients previously treated in the REGARD trial [3]. Recent research has focused on immunotherapy approaches, with the anti-PD-L1 agent pembrolizumab being the first immunotherapy approved for gastric cancer in pretreated patients in 2017 [4]. Nonetheless, despite major improvements, gastric cancer outcome remains with poor OS.

With many patients not responding to these treatments, several trials have explored different classification systems and biomarkers in attempts to early identify high risk patients, to better guide treatment decisions and to avoid unnecessary toxicity. In this regard, a radiological reevaluation performed after two chemotherapy cycles is recommended in hematological tumors, such as Hodgkin lymphoma [5]. This early assessment of response is related with OS and guide us to subsequent regimen in non-responsive tumors. In the molecular setting, a study by the Cancer Genome Atlas Research Network described four subtypes: microsatellite instability, chromosomal instability, genomically stable and Epstein-Bar virus positivity [6]. This molecular signature, as well as the model described by Singapore-Duke group [7] identifying mesenchymal, proliferative and metabolic groups, has been integrated into large molecular trials in reference laboratories, implicating expensive and advanced technology. However, while these molecular signatures were shown to be associated with OS outcome and prognosis, they have not been widely adopted in clinical practice given their cost and the non-availability of the required infrastructure in the majority of hospitals.

The immune system offers a source of alternative biomarkers, one of which is the neutrophil-to-lymphocyte ratio (NLR) which can be calculated from whole blood, and has been linked to the immune status of the patient. Recent investigations in the field of immunotherapy have focused on the importance of boosting the immune system by activating T lymphocytes to avoid immunotolerance [8,9], with different immune cells participating in this dynamic process. Neutrophils play an important role in carcinogenesis and recent research supports that they can promote tumor progression [10]. Therefore, the NLR may be a biomarker representing the balance between the patient's pro-tumor inflammatory status and anti-tumor immune status [11]. It has been studied as a personalized marker to stratify patients as a risk-based approach [12]. It has the added advantage of being both accessible and inexpensive. Several studies have evaluated NLR in the context of gastric cancer, most of which have focused on a single baseline determination [13-18]. However, in gastric cancer, dynamic measurement of NLR (i.e. before and during/after treatment), to determine change in NLR (c-NLR), has only been performed in patients with resectable-stage disease [19].

In this study, we evaluated bNLR and c-NLR in metastatic gastric cancer patients to explore its prognostic impact in terms of OS. We also propose a new score (DScore) with a potential predictive value to identify chemo-resistant patients and subsequently, to guide towards a new therapeutic treatment.

Methods

Ethical approval

This study complied with the Declaration of Helsinki and was approved by the Ethical Committee of Pontevedra-Vigo-Ourense, Spain (approval no.2017/382). Informed consent was signed from all patients who were alive at the study initiation. All laboratory tests, radiological evaluations and treatment procedures were performed as part of routine practice. Clinical data were obtained from medical records.

Cohort description and sample collection

In this ambispective study were analyzed data from 116 patients with metastatic gastric cancer at diagnosis who were treated at seven hospitals from Galician Research Group on Digestive Tumors (GITuD) between March 2009 and November 2019. Inclusion criteria were age >18 years, histologically confirmed gastric carcinoma, radiological or histological evidence of metastatic disease, administration of at least two cycles of chemotherapy as first-line treatment in the metastatic setting, no chemotherapy or radiotherapy within six months before starting chemotherapy for metastatic disease, no steroid treatment at baseline, no treatment with growth cell-stem factor (G-CSF) during the first two cycles and a normal complete blood count and data available in the electronic medical records. Patients were excluded if they had clinical evidence of inflammatory or infectious disease or incomplete follow-up data. Patient demographics (age, sex), clinical and disease characteristics at baseline were recorded including performance status (PS; Eastern Cooperative Oncology Group) at the time of diagnosis.

The chemotherapy regimens administered were based on doublets with fluoropyrimidines, except if contraindications existed. In this case, they received a doublet with taxane and platinum. Laboratory meas-

Table 1. Overall clinicopathological features of 116 patients with metastatic gastric cancer, and according to change of neutrophil-to-lymphocyte ratio

Characteristics	*Patients (n=116) n (%)*	*c-NLR (N=110)*		
		n (%)	*n (%)*	*p value*
		Decrease (74.5%) N= 82	*Increase (25.5%) N= 28*	
Age (years)				0.511
≤65	37 (33)	29 (35)	8 (29)	
>65	75 (67)	53 (65)	20 (71)	
Sex				0.511
Female	39 (34)	29 (36)	8 (28)	
Male	77 (66)	53 (64)	20 (72)	
ECOG performance status				0.070
0-1	67 (58)	52 (70)	12 (57)	
2	36 (31)	22 (28)	12 (37)	
Unknown	13 (11)	8 (2)	4 (6)	
Tumor location				0.450
Gastroesophageal junction	25 (22)	16 (21)	8 (29)	
Middle	56 (50)	43 (53)	11 (42)	
Antrum/pylorus	32 (28)	21 (26)	8 (29)	
Subtype				0.366
Intestinal	52 (45)	39 (48)	10 (36)	
Diffuse	37 (32)	24 (29)	11 (39)	
Mixed	14 (12)	11 (14)	2 (7)	
Unknown	13 (11)	8 (9)	5 (18)	
Visceral metastases				0.179
Yes	65 (56)	50 (61)	13 (46)	
No	51 (44)	32 (39)	15 (54)	
Peritoneal metastases				0.749
Yes	54 (47)	38 (46)	12 (43)	
No	62 (53)	44 (54)	16 (57)	
Node metastases				0.980
Yes	69 (59)	50 (61)	17 (60)	
No	47 (41)	32 (39)	11 (40)	
LDH (UI/L)				0.824
<450	73 (63)	52 (71)	18 (76)	
>450	27 (23)	18 (18)	7 (16)	
Unknown	16 (14)	15 (11)	4 (8)	
CEA (μg/L)				0.785
<10	70 (60)	48 (59)	17 (65)	
>10	43 (37)	32 (38)	10 (33)	
Unknown	3 (3)	2 (2)	1 (2)	
NLR baseline				0.066
<3.96	77 (66)	52 (63)	23 (82)	
≥3.96	39 (34)	30 (37)	5 (18)	
Chemotherapy regimen				0.066
Cisplatin -docetaxel	36 (32)	30 (36)	5 (18)	
5FU based	76 (68)	52 (64)	23 (82)	

LDH: lactate dehydrogenase; CEA: carcinoembryonic antigen; NLR: neutrophil-to-lymphocyte ratio; c-NLR: change neutrophil-to-lymphocyte ratio; 5FU: 5-fluorouracil

urements included lymphocyte, platelet and neutrophil counts. Laboratory data used blood samples collected before starting chemotherapy and after two chemotherapy cycles. In previous studies a range of incidence of neutropenia has been reported, so a blood sample was collected at the time of hematologic recovery to avoid myelosuppression. Radiological tumor response was assessed according to routine clinical practice (every 8 to 12 weeks) and it was determined according to RECIST 1.1. OS was defined as the time from the date of the first chemotherapy administration for metastatic disease until death from any cause. Patients who were still alive at the last follow-up were censored.

Data collection

All the enrolled patients had complete electronic medical record information, and their clinicopathological characteristics are summarized in Table 1.

The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. NLR was calculated at baseline and after two cycles of chemotherapy, in order to capture predictive tumor response as early as possible (and prior to radiological evaluation). Given the heterogeneity of thresholds proposed in previous studies, we chose the ROC method which established 3.96 as the optimal cut-off value. The c-NLR was calculated by subtracting baseline NLR from NLR after two cycles of chemotherapy.

The dynamic score (DScore) was calculated based on bNLR and c-NLR. Patients with high baseline NLR (≥ 3.96) and increase c-NLR (>0) were assigned as score 2. Patients with only one abnormal value were given a score 1. Patients with neither of these high values (low bNLR and decrease c-NLR) were characterized with score 0 (Table 2).

Statistics

Survival curves were estimated using the Kaplan-Meier method and compared by the log-rank test. Receiver operating characteristics (ROC) were performed to determine the optimal cut-off value for baseline NLR in terms of OS as 3.96. The baseline value was used to calculate the change in NLR (c-NLR), as NLR after two chemotherapy cycles minus NLR at baseline. Chi-square test was used to assess the relationship between c-NLR, DScore and the clinicopathological features of the patients. The relation between DScore and response to chemotherapy was determined using chi-square test. Univariate and multivariate analyses were performed to determine the significance of prognostic variables using the Cox proportional hazards models. A p value less than 0.05 was considered significant. Statistical analyses were carried out using SPSS software (v20.0).

Results

Patient population

In total, 116 patients with histologically-confirmed metastatic gastric carcinoma were eligible for analysis. The study cohort included 66% men with a median age of 68.7 years. Overall, 58% of the patients had ECOG PS 0-1 and 55.2% had two or more metastatic sites (Table 1). Most patients (66.4%) had a baseline NLR below 3.96. C-NLR was evaluable in 110 patients and a decrease in change NLR (c-NLR<0) was seen in 74.5%, while 25.5% had an increase in NLR (c-NLR>0). Analysis of clinicopathological characteristics according to c-NLR, revealed no statistical differences between patients in terms of c-NLR increase vs decrease (Table 1).

Relationship between NLR and survival

Patients were followed up for survival for a median of 8.70 months (95%CI 7.08 to 10.33). In univariate analysis, c-NLR and baseline NLR were both negative prognostic factors (Table 3). Baseline NRL ≥3.96 (5.97 vs 10.87 months, p=0.001) and change NLR >0 (6.63 vs 10.34 months, p=0.021) both correlated with poorer survival (Figure 1A and B), while borderline significance was seen for lactate dehydrogenase (LDH)>450 UI/L (5.02 vs 9.52, p=0.052) with poor OS. Other variables such as CEA >10 (5.91 vs 10.34 months, p=0.011) sex (male versus female); 7.68 vs 12.09 months, p=0.048) and performance status 2 vs 0-1 (4.63 vs 10.87 months, p=0.001) were also negative prognostic factors. Age, chemotherapy regimen, disease location and histology were not significantly related to prognosis (Table 3).

Clinically relevant variables with statistical significance were included in multivariate analysis. Increased c-NLR (HR=2.36, 95%CI: 1.35-4.13, p=0.003) and high baseline NLR (HR=2.16, 95% CI: 1.29-3.61, p=0.003) were strong negative prognostic factors for OS when adjusted by sex and PS and baseline CEA (Table 4a).

DScore as a prognostic factor for outcome

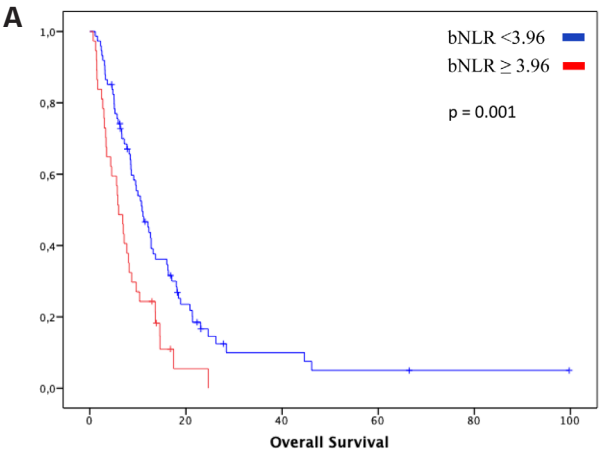
DScore was performed based on baseline NLR and c-NLR in three 'combination' categories (Table 2). Overall, 52 (44.8%) patients were classified as low risk or DScore 0, whereas 52 (44.8%) and 5 (4.31%) patients were classified as intermediate risk or DScore 1 and high risk or DScore 2, respectively. This was further analyzed in light of their significance in the multivariate analysis. Median OS was 12.74 vs 7.68 vs 2.43 months in these four groups, respectively (p<0.001; Table 3; Figure 1C).

Multivariate comparative analysis showed that compared to group DScore 0 (low risk), patients in group DScore 1 (HR: 1.83, 95% CI: 1.14-2.94, p=0.012), Dscore 2 (HR 9.62, 95% CI: 3.09-29.98, p<0.001), had a poorer prognosis, after adjustment for sex, and PS, and baseline CEA.

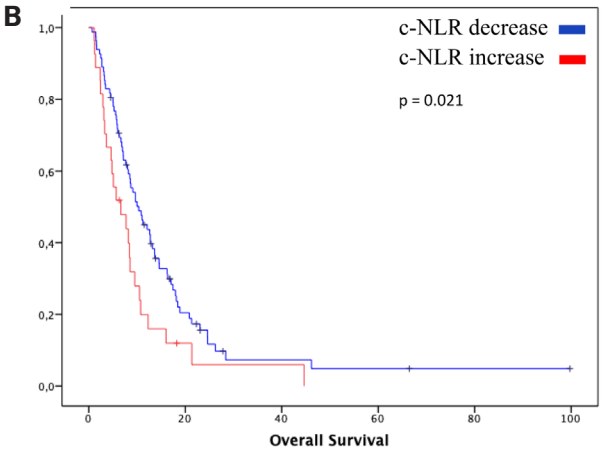
Table 2. Comparison of OS among various risk groups

Risk Group	*Risk*	*Patients, n*	*OS, months*	*p value*
Low risk: bNLR <3.96 and c-NLR <0	0	52	12.74	<0.001
Intermediate risk:				
- bNLR ≥3.96 and c-NLR < 0	1	52	7.68	
- bNLR <3.96 and c-NLR >0				
High risk: bNLR ≥3.96 and cNLR>0	2	5	2.43	

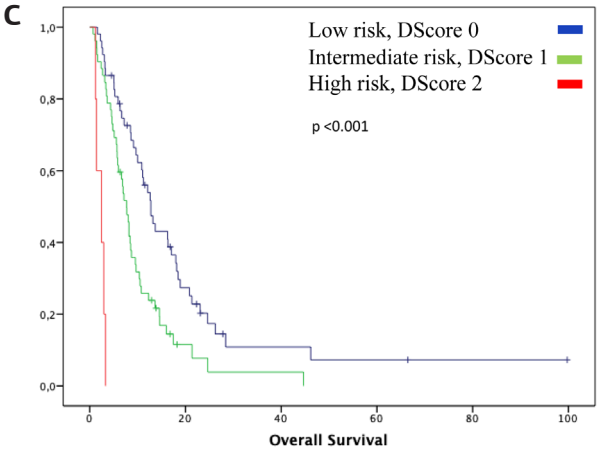
NLR: neutrophil-to-lymphocyte ratio; c-NLR: change of neutrophil-to-lymphocyte ratio, OS: overall survival



	bNLR ≥ 3.96	*bNLR <3.96*
Median OS, Months	5.97	10.87
(95% CI)	4.29-7.66	8.26-13.48



	c-NLR increase	*c-NLR decrease*
Median OS, Months	6.63	10.34
(95% CI)	2.37-10.90	7.14 – 13.55



	High risk, 2	*Intermediate risk, 1*	*Low risk, 0*
Median OS, Months	2.43	7.68	12.74
(95% CI)	0.17-4.68	6.36-9.01	10.07-15.42

Figure 1. Overall survival (OS) in patients with metastatic gastric cancer according to: **A:** baseline NLR; median OS for NLR ≥ 3.96 vs <3.96 cohorts was 5.97 vs 10.87 months, respectively (p=0.001). **B:** c-NLR; median OS of c-NLR increase vs decrease was 6.63 vs 10.34 months, respectively (p=0.021). **C:** DScore 0, 1 and 2 was 12.74, 7.68 and 2.43 months respectively (p<0.001).

Table 3. Univariate analysis of the association between clinicopathological features and survival

Characteristics	*OS Median (months)*	*95%CI*	*p value*
Age (years)			0.419
≤65	8.41	6.09 - 10.72	
>65	9.65	7.47 - 11.84	
Sex			0.048
Female	12.09	9.42 - 14.75	
Male	7.68	5.80 - 9.57	
ECOG performance status			0.001
0-1	10.87	8.29 - 13.46	
2	4.63	0.00 - 9.42	
Tumor location			0.180
Gastroesophageal junction	5.81	4.51 - 7.11	
Middle	9.65	6.74 - 12.57	
Antrum/pylorus	9.13	5.79 - 12.47	
Subtype			0.152
Intestinal	10.51	5.67 - 15.35	
Diffuse	6.63	5.33 - 7.93	
Mixed	8.70	5.96 - 11.44	
Unknown	9.65	6.92 - 12.39	
Visceral metastases (lung/liver)			0.101
Yes	9.65	7.54 - 11.77	
No	8.01	5.31 - 10.72	
Peritoneal metastases			0.730
Yes	9.13	7.27 - 10.99	
No	8.50	5.67 - 11.34	
Node metastases			0.138
Yes	8.50	6.52 - 10.49	
No	11.20	5.25 - 17.15	
LDH (UI/L)			0.052
<450	9.52	7.12 - 11.93	
>450	5.02	0.00 - 0.76	
CEA (μg/L)			0.011
<10	10.34	7.87 - 12.82	
>10	5.91	3.16 - 8.66	
NLR baseline			0.001
<3.96	10.87	8.26 - 13.48	
≥3.96	5.97	4.29 - 7.66	
Chemotherapy regimen			0.197
Cisplatin -docetaxel	9.65	7.87 - 11.44	
5FU Based	8.18	5.18 - 11.17	
NLR change (c-NLR)			0.021
Decrease	10.34	7.14 - 13.55	
Increase	6.63	2.37 - 10.90	
Vitamin D ng/mL			0.643
<20	10.74	5.39 - 16.09	
≥20	12.09	3.70 - 20.48	
PLR baseline			0.421
<160	9.65		
>160	8.01		

OS: overall survival; LDH: lactate dehydrogenase; CEA: carcinoembryonic antigen; NLR: neutrophil-to-lymphocyte ratio; c-NLR: change of neutrophil-to-lymphocyte ratio; CI: confidence interval

Dynamic score and response to chemotherapy

Overall, 71.2% of the patients who had a low bNLR and decreased c-NLR (DScore 0) responded to chemotherapy; however, disease progression was observed in 100% of patients with high bNLR plus increased c-NLR (DScore 2) (x^2=10.26, p=0.006; Table 4b).

Discussion

In this study, we found that baseline NLR and c-NLR were independent prognostic factors for OS in patients with metastatic gastric cancer who were treated with palliative chemotherapy. By combining both measures, the relation of DScore with prognosis and radiological response to chemotherapy was also demonstrated.

In recent years, research has focused on patient's inflammatory and immune responses, representing a new hallmark of cancer. Several studies have established the relation between inflammatory markers and prognosis in gastric and other solid tumors [12,18,20-22]. A range of immune cells participate in this response, which is a dynamic process, that furthermore can be modified by treatment. However, the main role of neutrophils in carcinogenesis is not completely understood. Neutrophils have been studied as a surrogate marker of this inflammatory reaction and they are a very important element in the metastatic cascade for extravasation and formation of premetastatic niches (accumulation of neutrophils in visceral organs before the arrival of metastatic cells) [23,24]. The baseline NLR reflects the balance between the host's immune response and the pro-tumor inflammatory reaction in a static point of the disease, which had prognostic value in our study. On the basis of our data, high baseline NLR (≥3.96) was shown to be a negative prognostic marker (5.97 vs 10.87 months, p=0.001) according to the published literature [25,26]. In multivariate analysis, baseline NLR was also related to OS (HR=2.16, 95% CI: 1.29-3.61, p=0.003).

Based on this dynamic scenario, a single determination of NLR may not be adequate to inform physicians about physiological modifications over time with chemotherapy, therefore we performed c-NLR. The NLR change after treatment is a significant factor to assess because it could reflect a variation in tumor and immune cells after chemotherapy. Hence, our hypothesis was based on the relation between the change in NLR after two cycles has prognostic value in terms of OS. Our study showed that an increase in the NLR after two cycles of first-line chemotherapy (c-NLR>0) was significantly related to poorer OS (HR=2.36, 95%CI: 1.35-4.13, p=0.003) in patients with metastatic gastric cancer, supporting that a change in NLR has a significant prognostic value, and that it is prognostic to a greater extent than a single baseline NLR determination. Previous studies have underlined the relation of change NLR with OS in different solid tumors, and our results are consistent with these trials. In patients with metastatic renal cancer treated with targeted therapy, Templeton et al demonstrated that early decline of NLR is associated with favourable prognosis [27]. Kim et al reported that change in NLR during chemotherapy in advanced ovarian cancer is an independent prognostic factor for progression-free survival (PFS). In that study, an increase NLR during chemotherapy

Table 4. A: Multivariate analysis c-NLR and bNLR, adjusted by sex, PS and CEA. **B:** Relation between DScore and chemotherapy radiological response

A *Variables*	*OS*	
	HR (95% CI)	*p value*
Sex (female/male)	1.92 (1.18 – 3.12)	0.009
Performance status (0-1/2)	1.97 (1.24 – 3.13)	0.004
Baseline NLR (<3.96/≥3.96)	2.16 (1.29 – 3.61)	0.003
c-NLR (decrease <0/increase >0)	2.36 (1.35 – 4.13)	0.003
CEA (<10/>10 μg/L	1.39 (0.86 – 2.27)	0.175

B *DScore*	*CR + PR + SD n (%)*	*PD n (%)*	x^2	*p value*
DScore 0: Low risk	37 (71%)	15 (29%)		
DScore 1: Intermediate risk	31 (59%)	22 (41%)	10.264	0.006
DScore 2: High risk	0 (0%)	5 (100%)		

CR: complete response; PR: partial response; SD: stable disease; PD: progression disease, x^2, OS: overall survival; HR: hazard ratio; LDH: lactate dehydrogenase; CEA: carcinoembryonic antigen; NLR: neutrophil-to-lymphocyte ratio; c-NLR: change in neutrophil-to-lymphocyte ratio

showed significantly poorer survival [28]. Furthermore, another study in biliary tract cancer by Cho et al showed that a dynamic change of increasing NLR and PLR during chemotherapy was associated with worse PFS and OS [29]. These results are also reported in early-stage pancreatic, gastric and colon cancer [30-33].

According to our results, longitudinal measurement of NLR provides not only more information about prognosis than baseline NLR, but also reflects the evolution of the patient's immune status and response to treatment. A decrease in c-NLR after chemotherapy was more frequent in patients with PS 0-1, those aged over 65 years, intestinal subtype, baseline LDH <450 IU/L, baseline NLR <3.96 and fluoropirimidines-based chemotherapy. Of note, the incidence of neutropenia associated with each regimen was considered irrelevant because blood samples were collected after hematologic recovery. On the basis of the results of baseline and change NLR as independent prognostic factors for OS, we performed an exploratory score that reflects the basal inflammatory situation and the dynamic change with chemotherapy. By combining both measures bNLR and c-NLR in DScore, patients were categorized in three groups. High risk group or DScore 2 significantly improved the prognosis (by over ten months) compared with low risk group or DScore 0 (median OS 12.74 vs 2.43 months, p<0.001). Intermediate risk group or DSCore 1 presented a median OS of 7.68 months. Combining baseline and change NLR (after two cycles) was investigated in a recent retrospective analysis in advanced pancreatic adenocarcinoma by Chen et al [34]. They categorized patients into four risk groups with significant prognostic value: group A (low baseline and decrease), group B (high baseline and increase), group C (low baseline and increase) and group D (high and increase) presenting a median OS of 15.2, 7.6, 6.8 and 3.8 months, respectively (p<0.001). Our findings reproduced this dynamic combination of NLR in metastatic gastric cancer and the results were consistent with previous studies in pancreatic cancer. Therefore, our results suggest that dynamic changes rather than a single baseline NLR could have more prognostic value in OS and effectively predict tumor response. The use of both NLR and c-NLR in DScore had stronger statistical weight for predicting OS when they are considered separately.

In addition to previous literature, we assessed the predictive value of DScore. High risk group or DScore 2 was related to worse response to chemotherapy (x^2=10.26, p=0.006), whereas only baseline NLR was not related to response, reflecting the fact that baseline NLR reflects only basal static disease situation, and not possible changes with treatment. This thus offers a potential mean of allowing patients likely to benefit from a favorable response to chemotherapy to be identified early (after two cycles of chemotherapy) from patients unlikely to benefit. Then, DScore may be considered as an stratification factor in future trials.

Potential limitation of the study is the small sample size and its ambispective nature.

The significant value of this study lies in the fact that – to the best of our knowledge – this is the first study to investigate the role of dynamic change in NLR as a prognostic and predictive biomarker in metastatic gastric cancer. This analysis allowed the identification of a relation between dynamic measurement of NLR (DScore) before and after two chemotherapy cycles and not only survival, but also with radiological response to chemotherapy. Given the relatively small sample size of this center study, prospective analyses and a large cohort are necessary to validate this hypothesis.

In conclusion, an increase in c-NLR after two cycles of chemotherapy and higher baseline NLR are negative independent prognostic factors (alone or combined) for outcome in metastatic gastric cancer. The significant relation between DSCore and response would guide physicians to assess early tumor radiological evaluation and to offer another effective chemotherapy treatment as in other hematological tumors. This unique combination biomarker of baseline NLR and c-NLR (DScore) may be considered as a new parameter to explore in future trials.

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Author's contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Antia Cousillas, Elena Gallardo Martin, Ana Fernandez Montes, Marta Carmona Campos, Marta Covela Rua, Mercedes Salgado, María Luz Pellon Augusto, Nieves Martinez Lago, Yolanda Vidal Insua, Elena Brozos, Juan De La Camara, Ana Alonso, Juan Carlos Mendez. The first draft of the manuscript was written by Antía Cousillas and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Competing interests

AFM reports personal fees from Amgen, Merck, Roche, Sanofi, Servier, Bayer, Lilly, BMS, EIsai outside the submitted work; ACC reports personal fees from Merck, Sanofi, Servier, Rovi outside the submitted work, JCMM, MEGM, MCC, MCR, YVI have nothing to declare, EMBV reports personal fees from Rovi and Leopharma outside the submitted work; JCG reports personal fees from Merck, Amgen, Roche, Sanofi outside the submitted work, MLPA reports personal fees from Roche and grants from Merck and Ipsen outside the submitted work; NML reports personal fees from Amgen, Merck, Roche, Sanofi, Lilly, BMS, Pfizer, Leopharma, Ipsen; MSF reports grants from Amgen, Servier, Merck, Roche, Sanofi and BMS outside the submitted work, AAH reports grants from Pfizer, Roche outside the submitted work.

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