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Prognostic value of neutrophil-to-lymphocyte ratio in advanced oesophago-gastric cancer: exploratory analysis of the REAL-2 trial

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Background: The REAL-2 trial demonstrated that capecitabine and oxaliplatin were effective alternatives to fluorouracil and cisplatin, respectively, when used in triplet chemotherapy regimens for previously untreated oesophago-gastric cancer. The aim of the current analysis was to evaluate the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) in the REAL-2 cohort.

Material and methods: A *post hoc* exploratory analysis was carried out on REAL-2 patients with the available absolute neutrophil count and absolute lymphocyte count. A high NLR was defined using a cut-off value of >3.0. The NLR was then correlated with clinical outcomes including overall survival (OS), progression-free survival (PFS) and objective response rate. Survival curves were generated using the Kaplan–Meier method and comparison between groups was carried out using Cox regression.

Results: Data were available in 908 of the 1002 REAL-2 participants. Of these, 516 (56.8%) were deemed to have a high NLR. In univariate analysis, high NLR was associated with a hazard ratio (HR) for OS of 1.73 (1.50–2.00), $P < 0.001$, compared with low NLR, equating to median OS values of 9.1 [95% confidence interval (CI) 8.0–9.6] and 12.7 months (95% CI 10.8–14.4), respectively. The NLR remained highly significant for OS ($P < 0.001$) in a multivariate model including performance status, age, disease extent, presence of liver metastases and presence of peritoneal metastases. For PFS, high NLR was associated with an HR of 1.63 (1.41–1.87), $P < 0.001$, compared with low NLR in univariate analysis. No significant interaction was found between NLR status and treatment arm, 13% of all

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patients with low NLR achieving survival beyond 24 months compared with only 6% of patients with high NLR ($P < 0.001$).

Conclusion: Our results confirm that high NLR status had a significant negative prognostic effect in the REAL-2 trial population. Based on the multivariate analysis, this effect was independent of other known prognostic factors.

Key words: oesophago-gastric cancer, neutrophil-to-lymphocyte ratio, EOX, ECF, ECX, EOF

introduction

Oesophago-gastric cancer (OGC) affects more than 15 000 individuals in the UK every year, and represents one of the commonest causes of cancer death with 70%–85% of patients dying within 5 years of diagnosis [1]. This high mortality rate is primarily a consequence of late diagnosis and limited therapeutic options despite significant improvements in multidisciplinary care [2]. Furthermore, the incidence of oesophageal adenocarcinoma is rising over the past 20 years, with only 2000 cases in 1995 compared with 3800 cases in 2012. In addition to the ongoing search for more effective therapeutics, there is currently a lack of reliable prognostic markers that can guide decision making for an individual patient and aid clinical trial stratification.

The UK National Cancer Research Institute, phase III Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2 (REAL-2) trial demonstrated that capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin, respectively, in patients with previously untreated OGC [3]. Due to the avoidance of indwelling lines and their complications with use of capecitabine, these results established both EOX and ECX as standard-of-care options for patients with advanced OGC. In many centres, oxaliplatin is favoured over cisplatin due to the shorter infusion time and avoidance of the large volumes of hydration required to safely administer cisplatin.

It has been known for many years that chronic inflammation plays an important role in the development and progression of cancer [4]. Specifically in relation to OGC, tumours can not only develop at the sites of inflammation, such as Helicobacter pylori infection, but they can also trigger a regional immune response around the tumour. Through release of a range of inflammatory factors, the cancer promotes the formation of an inflammatory micro-environment that subsequently aids tumour progression and metastasis [5]. Neutrophil-to-lymphocyte ratio (NLR) represents an inexpensive marker of host inflammation. A high NLR has been recently demonstrated to be prognostic in the advanced disease setting for a variety of solid tumours, including OGC [6, 7]. Additionally, we have previously demonstrated that the NLR is able to predict the likelihood of discovering peritoneal and/or metastatic disease at the time of the staging laparoscopy for early-stage gastric and oesophageal adenocarcinoma [8].

This *post hoc* exploratory analysis was undertaken within the REAL-2 trial population and aimed to further evaluate the prognostic impact of the NLR within a large, prospectively collected, phase III trial dataset of patients with advanced OGC. We were also interested in evaluating whether there was any interaction between the NLR and treatment benefit from each of the four different chemotherapy regimens evaluated in this trial.

methods

patients and trial design

The trial design and eligibility criteria have been reported previously. The primary objective of the phase III REAL-2 study was to evaluate whether capecitabine and oxaliplatin are at least as effective as fluorouracil and cisplatin, respectively, in terms of overall survival (OS) (Current Controlled Trials number, ISRCTN51678883). Eligible patients were enrolled in the trial from 59 centres in the UK and two centres in Australia between June 2000 and May 2005. Following enrolment, patients were randomly assigned to receive one of four triplet therapies: epirubicin and cisplatin plus either fluorouracil (ECF) or capecitabine (ECX) or epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX).

The eligible population for the current exploratory analysis included all REAL-2 participants with available white blood cell (WBC), absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) data at the time of trial randomization (before commencement of therapy).

The NLR was calculated using the standard formula: NLR = ANC/ALC [6].

statistical methods

All REAL-2 participants for whom baseline WBC, ANC and ALC data were available were included in the analysis. It was planned to group patients into 'high' and 'low' NLR populations based upon a pre-defined cut-off value of 3.0. This cut-off was determined based on prior publications [9–12]. It was also planned to evaluate the median NLR in our population and evaluate whether this median value provided more accurate prognostication than the 3.0 cut-off. Kaplan–Meier methods were used to estimate and plot survival end points. A Cox proportional hazard model was used to assess association between baseline NLR and survival end points, with hazard ratios (HRs) being reported. Interactions between treatment group and NLR level were included in the Cox proportional hazard model to assess whether the treatment effect differed between the NLR groups. Multivariate Cox regression models were used to assess if NLR association was independent of other prognostic factors including age; sex; primary tumour site; eastern cooperative oncology group Performance Status (PS 0, 1 or 2); disease extent (locally advanced, metastatic); liver metastasis; peritoneal metastasis; and alkaline phosphate.

results

patients

A total of 1002 patients were enrolled in the previously reported REAL-2 trial. Ninety-four patients for whom there were no ANC/ALC data were excluded, leaving an eligible population of 908 patients for this exploratory analysis. The median baseline NLR within our population was 3.7. Using the pre-defined cut-off of 3.0, 516 patients (56.8%) were deemed to have a high NLR.

association of NLR with baseline variables

Table 1 shows baseline characteristics with comparison between the low NLR and high NLR populations. This table demonstrates

Table 1. Baseline characteristics of the study participants with comparison between the low (≤3) and high (>3) NLR populations

Group	NLR ≤ 3 (*N* = 392)		NLR > 3 (*N* = 516)		*P*-value
	n	%	*n*	%	
Treatment					
ECF	101	25.8	132	25.6	0.983
ECX	102	26.0	129	25.0	
EOF	95	24.2	129	25.0	
EOX	94	24.0	126	24.4	
WHO PS					
0–1	368	93.9	443	85.9	<0.001
2–3	24	6.1	73	14.1	
Age					
<60 years	157	40.1	199	38.6	0.650
≥60 years	235	59.9	317	61.4	
Gender					
Female	86	21.9	87	16.9	0.054
Male	306	78.1	429	83.1	
Site of primary					
Gastric	165	42.1	193	37.4	0.152
Oesophago-gastric	227	57.9	323	62.6	
Disease extent					
Locally advanced	102	26.0	101	19.6	0.021
Metastatic	290	74.0	415	80.4	
Type of tumour					
Adenocarcinoma	357	91.1	443	85.9	0.174
Squamous	30	77	58	11.2	
Other	5	1.3	11	2.1	
Number of metastases					
0 or 1	257	65.6	304	58.9	0.041
≥2	135	34.4	212	41.1	
Liver metastasis					
No	252	64.3	283	54.8	0.004
Yes	140	35.7	233	45.2	
Peritoneal metastases					
No	331	84.4	421	81.6	0.260
Yes	61	15.6	95	18.4	
Alkaline phosphatase					
<100 U/l	205	54.8	256	52.5	0.492
≥100 U/l	169	45.2	232	47.5	

that an NLR > 3 is significantly associated with other adverse prognostic outcomes including poorer WHO PS (2–3) ($P \leq 0.001$), greater disease extent ($P = 0.021$), increased number of metastatic sites ($P = 0.041$) and presence of liver metastases ($P = 0.004$).

association between NLR and patient outcomes

Using the pre-defined cut-off of 3.0, there was found to be a strong association between NLR level and OS. The HR for OS in patients with high baseline NLR was 1.73 [95% confidence interval (CI) 1.50–2.00; $P < 0.001$], compared with the group with low baseline NLR. The corresponding median OS values were 9.1 months (95% CI 8.0–9.6) in patients with NLR >3 and 12.7 months (95% CI 10.8–14.4) in patients with NLR ≤3. Figure 1 displays the Kaplan–Meier curves for OS for the two NLR groups.

Applying the median NLR value of 3.7 as a cut-off, the effect on OS was similar with an HR of 1.67 (95% CI 1.45–1.92; $P < 0.001$) in the high NLR group. As this HR is lower than that reported with the cut-off value of 3.0, this median cut-off does not appear to improve the prognostic accuracy. Further analyses were therefore undertaken using the pre-planned 3.0 cut-off only.

In relation to progression-free survival (PFS), the same trend was revealed as for OS with an HR of 1.63 (95% CI 1.41–1.87, $P < 0.001$) in those with a high baseline NLR compared with the low baseline NLR group. The corresponding median PFS values were 6.0 months (95% CI 5.4–6.4) and 8.1 months (95% CI 7.0–9.2), respectively. Figure 1B displays the Kaplan–Meier curves for PFS for the two NLR groups.

Objective response rates were similar for low and high NLR groups, being 47.3% and 42.5%, respectively (odds ratio 0.82; 95% CI 0.63–1.08, $P = 0.15$).

multivariate analysis

A Cox multivariable analysis model including the previously described factors, found that NLR, WHO PS, age, extent of disease, presence of liver or peritoneal metastases were all independent predictors of survival (Table 2). The number of metastatic sites did not reach statistical significance ($P = 0.105$). In this model, NLR was associated with an adjusted HR of 1.67 (95% CI 1.45–1.93) and had a stronger prognostic influence than all of the other evaluated variables apart from PS (HR 1.92; 95% CI 1.54–2.39).

association between NLR and benefit from chemotherapy

Table 3 displays the effect of the NLR on OS in each of the four different treatment groups included in the REAL-2 trial (ECF, ECX, EOF and EOX). The HR ranges were similar in all four groups, ranging from 1.56 in the ECX population to 1.97 in patients receiving EOX. The interaction test revealed a *P* value of 0.55, suggesting no evidence of a significant interaction between NLR value and benefits from a specific regimen. These results confirm that the NLR value does not have a predictive role in relation to treatment selection in our population.

long-term survivors

There were 82 long-term survivors, defined as patients surviving beyond 24 months. Of these, 51 (62%) had low NLR compared with 31 (38%) with high NLR. This equated to 13% of all patients, with a low NLR achieving survival beyond 24 months compared with only 6% of patients with a high NLR. A test of proportions provided good evidence of an association between low baseline NLR and long-term survival ($P < 0.001$) (Table 4).

discussion

The findings of our exploratory analysis confirm that a high baseline NLR was associated with poorer OS and PFS outcomes among REAL-2 trial participants with advanced OGC. In our study, we did not find any significant interaction between NLR value and the benefit associated with any of the individual treatment regimens evaluated. As such, the NLR does not appear to have any predictive value in this population and, therefore, does not alter the interpretation of the previously reported REAL-2 outcomes in an unselected OGC population [3]. One of the main strengths of our study is the fact that the data arise from

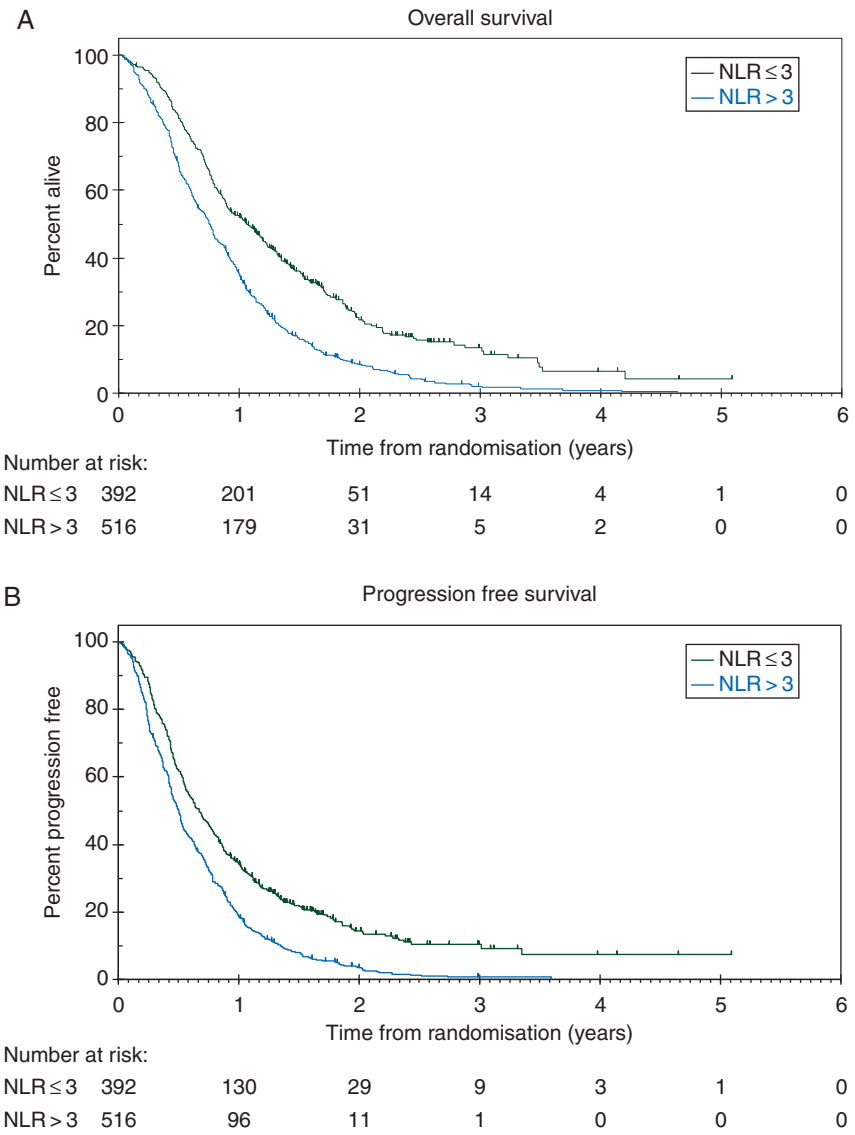

Figure 1. (A) Kaplan–Meier estimates of overall according to NLR level. (B) Kaplan–Meier estimates of progression-free survival according to NLR level.

within a prospectively maintained randomized phase III trial database. This represents one of the largest individual studies to evaluate the NLR in OGC and is a relatively homogeneous group of previously untreated patients. Based on the REAL-2 trial eligibility criteria, these patients are felt to be generally representative of the larger population of patients undergoing first-line treatment of advanced OGC. However, as with all phase III clinical trial data, those patients with a very poor prognosis or significant organ dysfunction will be under-represented.

Overall, the findings of this analysis are in keeping with the published literature, with a wealth of recent data across a wide range of solid organ tumours suggesting that inflammation-based prognostic indicators such as the NLR and the platelet lymphocyte ratio (PLR) are generally associated with poorer survival in cancer patient populations [6, 13]. In a systematic review and meta-analysis of NLR data from 100 studies and a total of 40 559 patients with various solid tumours, the results demonstrated that a higher NLR was associated with an adverse OS outcome (HR 1.81; 95% CI 1.67–1.97; $P < 0.001$) [6]. Furthermore, this effect was observed across all disease subgroups, tumour sites and stages of disease. Similar results were demonstrated with the PLR in a smaller meta-analysis conducted by the same authors [13]. Utilizing data from 12 754 patients within 20 studies, higher PLR was associated with significantly worse OS (HR 1.87; 95% CI 1.49–2.34); $P < 0.001$).

The NLR and the PLR serve as surrogate markers for an underlying pro-inflammatory tumour micro-environment, though the exact mechanisms by which this process leads to poorer cancer outcomes remain uncertain. It is known that the tumour micro-environment can attract, educate and control invading leucocytes to promote neo-angiogenesis, and increase cell viability, motility and invasion [14]. Neutrophils may act as tumour-promoting leucocytes through production of transforming growth factor-β, interleukin 10 and induction of regulatory T-cell pathways which inhibit the normal cytotoxic response. Circulating neutrophils may also directly secrete a

Table 2. Overall survival multivariate model

	Hazard ratio	95% Confidence interval	*P* value
NLR			
≤3	1.0		
>3	1.67	1.45–1.93	<0.001
WHO PS			
0–1	1.0		
2–3	1.92	1.54–2.39	<0.001
Age			
<60 years	1.0		
≥60 years	0.85	0.74–0.98	0.029
Disease extent			
Locally advanced	1.0		
Mets	1.24	1.01–1.52	0.036
Liver metastasis			
No	1.0		
Yes	1.33	1.13–1.57	0.001
Peritoneal metastases			
No	1.0		
Yes	1.57	1.29–1.91	<0.001

number of pro-oncogenic factors such as vascular endothelial growth factor, hepatocyte growth factor and interleukins [15–17]. For these reasons, the stroma around solid organ tumours has been compared with a poorly healing wound with the persistence of a wide range of chronic inflammatory processes [18]. In addition to processes which may increase the neutrophil count, a high NLR may also result from a relatively depleted lymphocyte count. In this scenario, the NLR value may be reflective of an impaired host immune response to malignancy, allowing the cancer growth to continue relatively unchecked. Indeed, the converse has been widely reported to be the case—that tumours with a significant infiltration of lymphocytes are associated with a better cytotoxic response and improved survival outcomes [19, 20].

The main limitation of our analysis is the fact that it is being carried out *post hoc*, with multiple comparisons that were not pre-specified in the study protocol or the original statistical plan. For this reason, the current findings are regarded as entirely exploratory. Another limitation is the lack of serial NLR values for each patient during their first-line chemotherapy. While the baseline NLR is undoubtedly of prognostic value, there are now additional data suggesting that increases or decreases in the NLR during treatment may also be of importance. In particular, data from a couple of published series have suggested that normalization of a high baseline NLR value during chemotherapy is associated with significant improvements in OS or PFS when compared with those with a persistently high NLR value throughout [21, 22]. As a dynamic marker, serial measurements during treatment could potentially help to identify those patients who are not deriving benefit from chemotherapy at an early time point. This requires further evaluation in ongoing trials where samples and data can be collected and analysed prospectively.

Table 4. Association of NLR with long-term survivorship (>24-month survival)

Group	NLR ≤ 3 (*N* = 392)		NLR > 3 (*N* = 516)		*P*-value
	n	%	*n*	%	
Long-term survivor					
≤24 months	341	87.0	485	94.0	<0.001
>24 months	51	13.0	31	6.0	

A further important limitation of all of the available data regarding NLR, including the current study, is the lack of consensus regarding the most appropriate cut-off for evaluation of the NLR. This is variably reported in the literature and, according to the meta-analysis findings, the median cut-off for the NLR in the reported studies is 4.0 for OS and 3.0 for PFS [6]. In our study, we had pre-specified at the time of formulating the statistical plan for this analysis that we would use a cut-off of 3.0 for all end points evaluated. However, using the median NLR value of 3.7 in our population did not add any additional prognostic value and was in fact associated with a lower HR for OS than the 3.0 cut-off. For the NLR to be useful as a baseline screening tool for clinicians, there needs to be consensus regarding the definitions of 'high' versus 'low' NLR. This would also greatly aid the use of the NLR as a stratification factor in future clinical trials.

In conclusion, a high NLR was negatively prognostic for both OS and PFS in patients with advanced OGC receiving first-line chemotherapy within the randomized phase III REAL-2 trial. A high NLR of >3 was associated with significantly shorter

Table 3. Efficacy of treatment stratified by NLR for each of the four chemotherapy regimens evaluated in the REAL-2 trial

NLR group	Treatment	Number of subjects	Number of events	Median OS	(95% CI)	Hazard ratio	(95% CI)	*P* value
ECF	≤3	101	80	12.0	9.8–14.2	1.0		
	>3	132	124	7.9	6.5–10.7	1.62	1.22–2.16	0.001
ECX	≤3	102	84	11.1	9.1–15.3	1.0		
	>3	129	121	9.6	8.3–11.0	1.56	1.17–2.07	0.002
EOF	≤3	95	75	14.7	10.3–16.8	1.0		
	>3	129	122	8.4	6.8–9.5	1.89	1.41–2.53	<0.001
EOX	≤3	94	65	14.3	9.9–18.9	1.0		
	>3	126	118	9.8	7.4–11.8	1.97	1.45–2.68	<0.001

P-value for interaction = 0.55.

survival across all four of the treatment regimens evaluated and was not found to have any role as a predictive biomarker in our dataset. The NLR could provide important additional prognostic information for patients and clinicians in daily practice and may be a relevant stratification factor in future clinical trials.

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disclosure

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