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A derived neutrophil to lymphocyte ratio predicts survival in patients with cancer

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BACKGROUND: The neutrophil lymphocyte ratio (NLR) has prognostic value in patients with a variety of cancers. Many chemotherapeutic trial databases hold information on white cell and neutrophil counts only. The aim of the present study was to compare the prognostic value of the NLR with a derived score (dNLR), composed of white cell and neutrophil counts.

METHODS: Patients ($n = 27\,031$) who were sampled incidentally between 2000 and 2007 for neutrophil, lymphocyte and white cell counts, and also had a diagnosis of cancer (Scottish Cancer Registry), were identified. Of this group, 12 118 patients who had been sampled within 2 years of their cancer diagnosis were studied.

RESULTS: On follow-up, there were 7366 deaths, of which 6198 (84%) were cancer deaths. The median time from blood sampling to diagnosis was 2.1 months. The area under the receiver-operating characteristic (ROC) curve for cancer-specific survival was 0.650 for the NLR and 0.640 for the dNLR. The NLR and dNLR were independently associated with survival in all cancers studied (all $P < 0.001$). The optimal thresholds, on the basis of hazard ratios and area under the curve, were 4 : 1 for the NLR and 2 : 1 for the dNLR.

CONCLUSION: The results of the present study show that the dNLR has similar prognostic value to the NLR. Therefore, the universally available dNLR is to be commended for use in the risk stratification of patients undergoing chemotherapy.

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Cancer incidence is increasing in the United Kingdom, the United States and worldwide (Ferlay, 2010). Although it is clear that the development of cancer has a genetic basis, recent work has demonstrated that the host inflammatory response plays an important role in carcinogenesis and disease progression (Colotta *et al*, 2009; Hanahan and Weinberg, 2011).

It is therefore of interest that the combination of haematological components of the systemic inflammatory response, specifically neutrophils and lymphocytes, termed the neutrophil lymphocyte ratio (NLR) have been shown to have prognostic value in patients with a variety of cancers (Walsh *et al*, 2005; Cho *et al*, 2009; Sarraf *et al*, 2009; Shimada *et al*, 2010; Azab *et al*, 2011; Sharaiha *et al*, 2011), as well as patients undergoing chemotherapy for cancer (Kao *et al*, 2010; Chua *et al*, 2011). Although, apparently inferior to other measures of the systemic inflammatory response, such as the mGPS (Proctor *et al*, 2011a), the NLR does have the advantage of its components being inexpensive and routinely measured in day-to-day oncological practice, and in current chemotheraputic cancer trials. Clearly, if such extensive data were to confirm the prognostic value and clinical utility of the NLR, this would be an important, relevant, clinical translational advance in the identification of cancer patients at high risk (Clarke *et al*, 2011).

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However, on patient entry to chemotherapeutic trials, despite having a differential white cell count carried out, only white cell and neutrophil counts are routinely entered into clinical trial databases. In an attempt to obviate this problem and allow the widespread utilisation of a similar inflammation-based score in such settings, we aimed to investigate the prognostic value of a derived NLR (dNLR), from a white cell and neutrophil count. Therefore, the aim of the present study was to compare the prognostic value of the NLR and dNLR adjusted for age, sex, deprivation and tumour site in the Glasgow Inflammation Outcome Study (GIOS).

PATIENTS AND METHODS

Study design

From the GIOS cohort previously described (Proctor *et al*, 2010), patients who had samples including a differential white cell count (white cell count, neutrophil count and lymphocyte count) were included. At the time of data collection, the Scottish Cancer Registry (SCR) held complete pathological and clinical cancer diagnosis records from 1 January 1980 until 31 December 2007, and mortality follow-up until 30 June 2009. Deaths were classed as cancer-specific if the primary cause of death matched the primary cancer diagnosis. Otherwise, deaths were classed as non-cancer-specific. Cancer stage data was obtained from the SCR where available.

Table 1 The relationship between patient characteristics, tumour site, and overall and cancer-specific survival in all patients

		n = 12 118 (%)	5-year overall survival % (*n* of deaths) *n* = 7366	*P*-value	5-year cancer specific survival % (*n* of deaths) *n* = 6198	*P*-value
Age	<65 years	5423 (45)	50 (2571)		54 (2314)	
	65–74 years	3673 (30)	32 (2412)		39 (2041)	
	⩾75 years	3022 (25)	20 (2383)	<0.001	30 (1843)	<0.001
Sex	Male	5900 (49)	28 (4094)		35 (3435)	
	Female	6218 (51)	46 (3272)	<0.001	52 (2763)	<0.001
SIMD 2006	1 (least deprived)	1697 (14)	48 (859)		54 (731)	
	2	1485 (12)	45 (780)		51 (654)	
	3	1804 (15)	42 (1011)		48 (866)	
	4	2439 (20)	34 (1541)		42 (1284)	
	5 (most deprived)	4693 (39)	30 (3175)	<0.001	38 (2663)	<0.001
Tumour site	Breast	2147 (18)	78 (442)		84 (304)	
	Bladder	562 (5)	48 (286)		62 (195)	
	Gynaecological	639 (5)	47 (325)		53 (281)	
	Prostate	709 (6)	51 (323)		64 (222)	
	Gastroesophageal	1085 (9)	11 (932)		14 (851)	
	Haematological	1209 (10)	47 (625)		58 (454)	
	Renal	552 (4)	18 (324)		44 (285)	
	Colorectal	1413 (12)	39 (820)		46 (680)	
	Head and Neck	738 (6)	35 (452)		52 (296)	
	Hepatopancreaticobiliary	721 (6)	6 (660)		7 (626)	
	Pulmonary	2343 (19)	6 (2177)	<0.001	8 (2004)	<0.001

Abbreviation: SIMD = Scottish Index of Multiple Deprivation.

Patients with blood samples taken within 2 years of their cancer diagnosis were included in the analysis, and split into those sampled before and following cancer diagnosis. The dNLR was derived from the assumption that the white cell count is made up primarily of lymphocytes and neutrophils, and therefore, the white cell count minus the neutrophil count would be broadly similar to the lymphocyte count. As different thresholds have been suggested in the past (Ding *et al*, 2010; Kim *et al*, 2010; Ohno *et al*, 2010; Sharaiha *et al*, 2011), several were examined to ascertain the optimal NLR and dNLR.

Patient inclusion criteria has been previously detailed and only cancer groups previously studied were included (Proctor *et al*, 2010). Ethical approval was granted for the present study by the Research Ethics Committee, North Glasgow NHS Trust.

Methods

The North Glasgow haematological database was searched to obtain patients with white cell, neutrophil and lymphocyte counts. The NLR was constructed as follows: NLR = neutrophil count to lymphocyte count. The dNLR was constructed as follows: dNLR = neutrophil count to (white cell count − neutrophil count).

International Classification of Disease 10 codes were used to identify the site of cancer diagnosis as previously described (Proctor *et al*, 2010). The Scottish Index of Multiple Deprivation (SIMD) 2006, as recommended by the Information Services Division on behalf of NHS Scotland and the Scottish Government Department of Health, was used to measure deprivation with the least deprived being scored as 1 to the most deprived scoring 5 (Bishop *et al*, 2004).

Statistics

Survival, overall and cancer-specific, was calculated from the time of cancer diagnosis to death. Kaplan–Meier estimator was used to analyse the relationship between patient characteristics, tumour site, and overall and cancer-specific survival (Table 1).

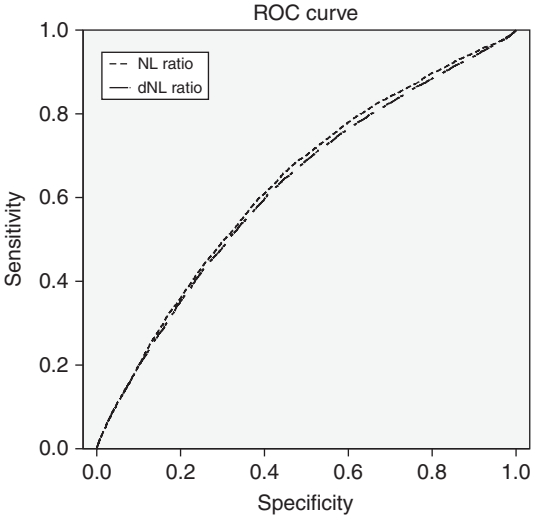

Figure 1 Receiver-operating characteristic curve for cancer-specific survival.

Receiver-operating characteristic (ROC) curve was used to determine the sensitivity and specificity similarities between the NLR and dNLR (Figure 1). Cox proportional multivariate regression analysis, corrected for age, sex, deprivation and tumour site, as well as area under the ROC curve, were used to determine the relationship between different NLR and dNLR thresholds (in whole numbers) and survival in patients sampled before and after diagnosis (Table 2). Box plot was used to demonstrate the relationship between the NLR, dNLR and Dukes stage in patients with colorectal cancer (Figure 2). Cox proportional multivariate regression analysis, corrected for age, sex, deprivation and tumour site, as well as area under ROC curve, were used to determine the relationship between optimal NLR and dNLR thresholds,

Table 2 The relationship between NLR and dNLR thresholds, and survival. Adjusted for age, sex, deprivation and stratified by tumour site

			Overall survival			Cancer-specific survival		
	Ratio	***n* (%)**	**HR**	***P*-value**	**AUC**	**HR**	***P*-value**	**AUC**
Patient sampled prior to cancer diagnosis, n = 3859								
NLR	<1:1	78 (2)	1			1		
	⩾1:1	3781 (98)	1.03	0.840	0.507	0.967	0.859	0.507
	<2:1	589 (15)	1			1		
	⩾2:1	3270 (85)	1.49	<0.001	0.563	1.48	<0.001	0.547
	<3:1	1354 (35)	1			1		
	⩾3:1	2505 (65)	1.55	<0.001	0.593	1.52	<0.001	0.560
	<4:1	1987 (51)	1			1		
	⩾4:1	1872 (49)	1.57	<0.001	0.598	1.52	<0.001	0.558
	<5:1	2435 (63)	1			1		
	⩾5:1	1424 (37)	1.50	<0.001	0.579	1.44	<0.001	0.542
dNLR	<1:1	214 (6)	1			1		
	⩾1:1	3645 (94)	1.17	0.098	0.518	1.16	0.163	0.516
	<2:1	1399 (36)	1			1		
	⩾2:1	2460 (64)	1.54	<0.001	0.593	1.53	<0.001	0.563
	<3:1	2461 (64)	1			1		
	⩾3:1	1398 (36)	1.47	<0.001	0.575	1.43	<0.001	0.543
	<4:1	2960 (77)	1			1		
	⩾4:1	899 (23)	1.46	<0.001	0.552	1.41	<0.001	0.527
	<5:1	3267 (85)	1			1		
	⩾5:1	592 (15)	1.40	<0.001	0.538	1.33	<0.001	0.517
Patient sampled following cancer diagnosis, n = 8259								
NLR	<1:1	296 (4)	1			1		
	⩾1:1	7963 (96)	1.16	0.094	0.505	1.89	0.069	0.506
	<2:1	1480 (18)	1			1		
	⩾2:1	6779 (82)	1.63	<0.001	0.575	1.67	<0.001	0.566
	<3:1	2984 (36)	1			1		
	⩾3:1	5275 (64)	1.85	<0.001	0.641	1.93	<0.001	0.629
	<4:1	4104 (50)	1			1		
	⩾4:1	4155 (50)	1.86	<0.001	0.661	1.92	<0.001	0.646
	<5:1	4872 (59)	1			1		
	⩾5:1	3387 (41)	1.82	<0.001	0.657	1.86	<0.001	0.642
dNLR	<1:1	655 (8)	1			1		
	⩾1:1	7604 (92)	1.35	<0.001	0.521	1.39	<0.001	0.519
	<2:1	3083 (37)	1			1		
	⩾2:1	5176 (63)	1.76	<0.001	0.630	1.83	<0.001	0.620
	<3:1	4978 (60)	1			1		
	⩾3:1	3281 (40)	1.74	<0.001	0.644	1.78	<0.001	0.631
	<4:1	6034 (73)	1			1		
	⩾4:1	2225 (27)	1.75	<0.001	0.619	1.78	<0.001	0.609
	<5:1	6632 (80)	1			1		
	⩾5:1	1627 (20)	1.76	<0.001	0.595	1.80	<0.001	0.589

Abbreviations: AUC = area under receiver-operating characteristic curve; dNLR = derived NLR; HR = hazards ratio; NLR = neutrophil lymphocyte ratio. Shaded values signify the optimal thresholds.

and survival in patients with advanced (Dukes C and D) colorectal cancer (Table 3). Analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA).

RESULTS

From the GIOS cohort of 223 303 patients previously described (Proctor *et al*, 2010), 27 031 patients were identified as also having a diagnosis of cancer. Within this group, 12 118 patients had been sampled within 2 years of their cancer diagnosis. Of this group, 3859 (32%) were sampled before a diagnosis and 8259 (68%) were sampled following diagnosis, and the possible initiation of surgical or chemotherapeutic interventions.

The majority of patients were under the age of 75 years ($n = 9096$, 75%), were female ($n = 6218$, 51%) and were from the most deprived SIMD quintile ($n = 4693$, 39%). The minimum follow-up from cancer diagnosis was 18 months and the maximum 132 months (median 52 months for survivors).

The relationship between patient characteristics, tumour site, and overall and cancer-specific survival in all patients is shown in Table 1. In total, 12 118 patients were studied. On follow-up, there were 7366 deaths of which 6198 (84%) were cancer-related. The median time from blood sampling to diagnosis was 1.6 months in those sampled before diagnosis and 2.2 months in those sampled following diagnosis, suggesting that most scores reflect status at diagnosis. Increasing age, male gender and increasing deprivation were associated with reduced 5-year overall and cancer-specific survival (all $P < 0.001$).

The ROC curves, using cancer-specific death as an end-point ($n = 12\,118$) for NLR and dNLR is shown in Figure 1. The ROC curves for NLR and dNLR were 0.650 ($P < 0.001$) and 0.640 ($P < 0.001$), respectively. The Spearman rank correlation between the NLR and dNLR was 0.962 ($P < 0.001$).

The relationship between NLR and dNLR thresholds and survival in patients sampled before and following diagnosis, adjusted for age, sex and deprivation, and stratified by tumour site, is shown in Table 2. The optimal thresholds for the NLR (⩾4:1) and the dNLR (⩾2:1) in both patients sampled before and following diagnosis, as measured by the hazard ratios and area under the ROC curve, are highlighted.

In the present cohort, a limited number of patients had stage-related data available in the SCR, with only colorectal cancer having stage data for over 50% of patients. Stage was only available in 29% ($n = 621$) of patients with breast cancer and 10% ($n = 234$) of patients with pulmonary cancer. Other cancer groups had no stage available. Of the colorectal cancer patients with stage available, 90 (9%) were Dukes A, 264 (27%) were Dukes B, 327 (33%) were Dukes C and 312 (31%) were Dukes D.

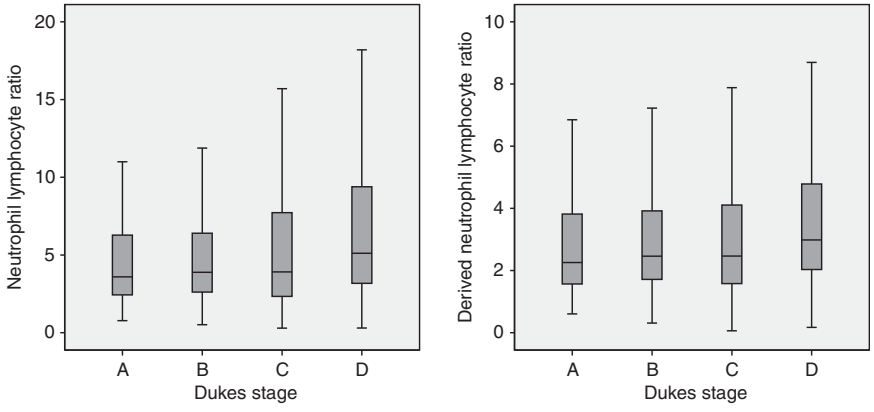

Figure 2 The relationship between NLR, dNLR and Dukes stage in patients with colorectal cancer.

Table 3 The relationship between the NLR, dNLR and survival in patients with advanced colorectal cancer (Dukes C and D). Adjusted for age, sex and deprivation

		Overall survival				Cancer-specific surviva		
		***n* = 639 (%)**	**HR**	***P*-value**	**AUC**	**HR**	***P*-value**	**AUC**
NLR	<4:1	278 (44)	1			1		
	⩾4:1	361 (56)	1.60	<0.001	0.584	1.60	<0.001	0.565
dNLR	<2:1	194 (30)	1			1		
	⩾2:1	445 (70)	1.61	<0.001	0.575	1.67	<0.001	0.566

Abbreviations: AUC = area under receiver-operating characteristic curve; dNLR = derived NLR; HR = hazards ratio; NLR = neutrophil lymphocyte ratio.

The relationship between the NLR, dNLR and Dukes stage in all patients is shown in Figure 2. The relationship between the NLR, dNLR and survival in patients with advanced colorectal cancer (Dukes C and D) adjusted for age, sex and deprivation is shown in Table 3. These patients were studied, as they are likely to be similar to those entered into chemotherapeutic trials (Chua *et al*, 2011). On survival analysis ($n = 639$), both the NLR and dNLR were associated with reduced overall and cancer-specific survival independent of age, sex and deprivation (all $P < 0.001$), with similar hazard ratios and area under the ROC curve (both $P < 0.001$).

DISCUSSION

The results of the present study show clearly that the NLR and dNLR have similar prognostic value, and that they can be used similarly to predict survival in a large cohort of unselected cancer patients. Furthermore, the NLR and dNLR had similar predictive value, in all cancers as well as advanced colorectal cancer. Recently, Chua *et al* (2011) reported that the NLR, as a marker of the systemic inflammatory response, predicted clinically meaningful outcomes in patients with advanced colorectal cancer and receiving chemotherapy. Taken together, these results would indicate that the derived NLR is suitable for the examination of risk stratification of patients in chemotherapeutic trials, in particular, colorectal cancer studies.

In the present study, although the ROC analysis of the NLR and dNLR were similar, the prognostic value of different thresholds was examined. It was of interest that in contrast to the most commonly used NLR threshold of 5:1 (Walsh *et al*, 2005; Gomez *et al*, 2008; Halazun *et al*, 2008), in the present study, 4:1 was found to have superior prognostic value in terms of hazard ratio and area under the ROC curve. These results are consistent with the varying NLR threshold reported across and within different tumour types. It is also of interest that the optimal threshold for the dNLR was 2:1, an expected shift from that of the NLR explained by the method of derivation. The results of the present study also suggest that the dNLR has considerable potential to be adopted universally as a stratification factor in all current cancer clinical trials. Moreover, if it were shown to have such clinical utility, the dNLR would identify patients who may respond to anti-inflammatory interventions.

In the present study, it was of interest that there was a small but persistent superiority of the prognostic value of the NLR over the dNLR. The basis of this observation is not clear. However, in the dNLR, the use of (WBC − neutrophil) in the denominator is broadly mixing two cell types, lymphocytes and monocytes, with possible opposing effects in terms of predictive value. In the normal range, the relative proportion of lymphocytes to monocytes is approximately 6:1. In cancer patients, there may be a fall in the absolute proportion of lymphocytes and an increase in the absolute proportion of monocytes. Even so, their relative proportion is unlikely to fall below 3:1 even in advanced disease (Leitch *et al*, 2007). Therefore, WBC − neutrophil is dominated by lymphocytes and is likely to be a reasonable approximation to the lymphocyte fraction, and the potential error introduced by the presence of monocytes in the fraction is therefore likely to be small. Given that different aspects of the differential white cell count have been reported to predict survival (Leitch *et al*, 2007; Proctor *et al*, 2011b; Lee *et al*, 2012), it is possible to derive other ratios, such as the neutrophil : white cell count ratio. However, of the differential white cell count parameters, the neutrophil : lymphocyte ratio has been the most extensively validated, and it was this that we were attempting to recapitulate in the dNLR of the present study. Clearly, where the NLR is available, it should be used. However, there is a wealth of clinical trial data, where only white cell and neutrophil counts have been recorded in computer databases, which could be used to examine, in detail, the clinical value of the haematopoietic tissue-derived systemic inflammatory response. As the present study validates the use of the dNLR, this may help unlock the residual value of such clinical trial databases and encourage the widespread utilisation of a similarly based systemic inflammation-based scores in such settings.

The results of the present study also confirm the hypothesis that a total white cell count may be a useful addition to the currently established prognostic markers of the systemic inflammatory response, such as, C-reactive protein, albumin, neutrophil, and lymphocytes counts and their combinations (Proctor *et al*, 2011a). It was also of interest that the hazard ratios and areas under the curves were greater from patients sampled after diagnosis compared with patients sampled before diagnosis. These results would suggest that the systemic inflammatory response is a more potent stimulator of cancer progression in established disease. This is consistent with the long-standing observations on the 'seed and soil' nature of cancer progression and metastasis (Fidler and Poste, 2008).

The present cohort has a number of limitations. The patients were selected on the presence of haematological and biochemical variables, and were therefore not necessarily representative of all cancer patients in general. Patients may also have concurrent morbidity, including infection, causing alterations in their haematological variables. It is also recognised that demographic variables, such as race, that appear to influence neutrophil counts were not available. Nevertheless, the optimal prognostic threshold for the NLR in the range of 4–5:1 have been consistently validated in different cancer cohorts (Clarke *et al*, 2011). It remains to be determined whether a dNLR of 2:1 will be similarly validated in different cancer cohorts.

In summary, the results of the present study show that a dNLR, on the basis of a white cell and neutrophil counts, has similar prognostic value to the NLR. Therefore, the universally available dNLR is to be commended for use in the risk stratification of patients undergoing chemotherapy.

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Conflict of interest

The authors declare no conflict of interest.

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