Imaging, Diagnosis, Prognosis

Clinical Cancer Research

High Blood Neutrophil-to-Lymphocyte Ratio Is an Indicator of Poor Prognosis in Malignant Mesothelioma Patients Undergoing Systemic Therapy

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Abstract

Purpose: Asbestos-induced chronic inflammation is implicated in the pathogenesis of malignant mesothelioma (MM). We have investigated blood neutrophil-to-lymphocyte ratio (NLR), an index of systemic inflammation, as a prognostic factor in MM patients.

Experimental Design: Patients with MM who had systemic therapy at participating institutes were studied. Potential prognostic factors such as age, gender, performance status, histologic subtype, and baseline laboratory parameters, including NLR, were analyzed. Overall survival from commencement of therapy was determined by the Kaplan–Meier method. Multivariate analyses using Cox Regression model were performed with significant factors ($P \leq 0.05$) to determine their independent effect.

Results: A total of 173 MM patients undergoing systemic therapy including 119 patients receiving first-line therapy and 54 patients receiving second- or third-line therapy were included in this retrospective evaluation. Forty-two percent of patients had an elevated NLR at baseline. The following variables were predictive of survival: female gender ($P = 0.044$), epithelioid histologic subtype ($P < 0.001$), baseline white blood cell count less than 8.3×10^9/L ($P = 0.008$), baseline platelet count 400×10^9/L or less ($P = 0.05$), and NLR of 5 or less ($P < 0.001$). After multivariate analysis, histologic epithelioid subtype [hazard ratio (HR) = 2.0; 95% confidence interval (CI) = 1.3–2.9; $P = 0.001$], and NLR less than 5 (HR = 2.7; 95% CI = 1.8–3.9; $P < 0.001$) remained independent predictors. The 1-year survival rate was 60% versus 26%, whereas the 2-year survival rate was 34% versus 10% for NLR less than 5 and 5 or greater, respectively. In the separate analyses of chemotherapy-naive and previously treated patient groups, NLR was an independent predictor of survival in both groups.

Conclusion: Our results indicate that NLR is an independent predictor of survival for patients with MM undergoing systemic therapy. *Clin Cancer Res; 16(23); 5805–13. ©2010 AACR.*

Malignant mesothelioma (MM) is an aggressive, asbestos-related neoplasm that arises from the mesothelium, a membrane lining the serosal cavities (1). Previously rare, MM is increasing in incidence in developed countries (2), but because of the continued widespread use of asbestos in developing countries (3), MM will remain a worldwide health issue in the ensuing decades. Furthermore, MM remains an invariably fatal disease, with a median survival ranging from 7 to 24 months depending on the stage of the disease and modalities of treatments used (4–6).

Despite a very poor overall prognosis for patients with MM, some patients live with their disease for a considerable period of time. Currently, 2 composite scoring systems devised by the European Organisation for Research and Treatment of Cancer (EORTC) and the Cancer and Leukemia Group B (CALGB) are used to predict outcomes for MM patients. The EORTC found that performance status, white blood cell (WBC) count, gender, histologic subtype, and whether the histologic diagnosis was definitive or not were significant prognostic factors. On the basis of these variables, they were able to stratify patients into either good, with 1-year survival rate of 40%, or poor prognosis groups, with 1-year survival rate of 12% (7). The CALGB used exponential survival tree analysis with prognostic variables of performance status, age, WBC count, hemoglobin, presence or absence of weight loss, and chest pain and defined 6 groups of patients with varying median survival times ranging from 1.4 to 13.9 months (8).

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Translational Relevance

We have identified that the ratio of neutrophils to lymphocytes from a simple full blood count can identify patients with malignant mesothelioma with good or poor prognoses with a survival difference of almost 10 months. This finding will alter the management of this condition and the test can be performed inexpensively anywhere in the world. These data also highlight the importance of the inflammatory response in influencing cancer prognosis and emphasize that this should be an important focus of cancer research in the future.

However, these systems are not used routinely because they are relatively unwieldy and thus their use is largely confined to the clinical trial setting to stratify patient cohorts so that treatment results can be appropriately interpreted and compared. An easily reproducible and inexpensive marker that could better estimate the prognosis of patients with MM would be of substantial value for clinicians involved in the treatment of MM and for determining appropriate levels of compensation for those who developed MM after occupational asbestos exposure.

Inflammation seems to play a critical role in the development and progression of numerous cancers, including MM. A variety of infectious agents and environmental toxins produce the chronic tissue damage that leads to the local inflammatory reactions in these malignancies, with asbestos fibers the principal issue in MM. Tumor development and progression induced by an inflammatory response is thought to be mediated by an interaction between proinflammatory cytokines and pathways including NF-κB and STAT3 (9). In addition to promoting tumor growth, the release of proinflammatory cytokines can produce systemic inflammatory symptoms such as fever, sweats, and weight loss and result in the release of acute-phase proteins from the liver that can be measured in plasma.

It has been postulated that markers of systemic inflammation may provide useful information for prognostication. Various markers of systemic inflammatory response, including cytokines, C-reactive protein (CRP), modified Glasgow prognostic score (mGPS), which combines CRP and albumin, and absolute WBC count as well as its components such as neutrophil-to-lymphocyte ratio (NLR) have been investigated for their prognostic role in some cancer populations (10, 11). However, the prognostic role of inflammatory markers in MM has not been studied previously. We hypothesized that patients with MM with an elevated NLR would have a shorter survival, given their exaggerated systemic inflammatory response.

The aim of this study was to investigate the potential relationship between NLR and prognosis in a retrospective series of MM patients undergoing systemic therapy. Further exploratory analyses evaluated the impact of normalization of NLR following 1 cycle of systemic therapy on overall survival (OS) and the predictive value of a variety of inflammatory markers and cytokines on survival in a subtype of MM patients.

Materials and Methods

Study patients

Consecutive MM patients who had been commenced on chemotherapy from January 2004 to February 2009 at Sydney Cancer Centre as well as MM patients who had been enrolled on clinical trials since 1999 at Sydney Cancer Centre and Royal North Shore Hospital, St Leonards, New South Wales, were included in this study. Treatment groups are summarized in Table 1. The group is divided into chemotherapy-naive patients and previously treated patients. Figure 1 shows the study flow chart. Patients in the retrospective series were followed at the discretion of the treating oncologist: before each cycle of chemotherapy and then approximately every 6 weeks until death. Patients enrolled in clinical trials were followed as per the trial protocol until death.

This study was approved by the Human Research Ethics Committees at the Sydney South West Area Health Service—Concord Zone and Royal Prince Alfred Hospital Zone.

Baseline variables

Patient characteristics, tumor-related details, baseline symptoms, and laboratory parameters were examined as potential prognostic factors. These included age (<65 vs. ≥65 years), gender (male vs. female), ECOG performance status (0 vs. ≥1; ref. 7, 8), histologic subtype (epithelioid vs. nonepithelioid; ref. 8), clinical stage (I–II vs. III–IV; ref. 16), EORTC prognostic score (good vs. poor group; ref. 7), baseline WCC ($\leq 8.3 \times 10^9$/L vs. $>8.3 \times 10^9$/L; ref. 7), platelet count ($\leq 400 \times 10^9$/L vs. $>400 \times 10^9$/L; ref. 8), hemoglobin difference defined as the difference relative to 160 g/L in men and 140 g/L in women (<10 vs. ≥10 g/L; ref. 16), and NLR (<5 vs. ≥5).

NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. An NLR 5 or greater was considered elevated in accordance with earlier report (17–20). NLR was recorded at baseline and where available after 1 cycle of systemic therapy. All patients with abnormal NLR (≥5) at baseline were divided into 2 groups: patients with normalization of NLR (<5) and patients with persistently abnormal NLR following 1 cycle of systemic therapy.

Whenever possible, clinical stage was recorded according to the American Joint Committee on Cancer Staging System (21).

The EORTC prognostic score used WBC count of 8.3×10^9/L or greater, ECOG performance status of 1 or greater, sarcomatoid histologic subtype, probable or possible histologic diagnosis, and male gender as poor prognostic

Table 1. Patient groups included in this study

	Phase	Therapy	No. of patients
Patients having participated in first-line protocol treatments ($n = 119$)			
Sydney Cancer Centre (12)	Retrospective	Carboplatin + pemetrexed	51
		Cisplatin + pemetrexed	8
		Pemetrexed	4
		Carboplatin + gemcitabine	4
		Gemcitabine	1
Emphasis (4)	III	Cisplatin vs. cisplatin + pemetrexed	17
Thalidomide—arm A (13)	Parallel Phase II	Thalidomide in combination with cisplatin + gemcitabine	34
Patients studied in second/third-line setting ($n = 54$)			
Imatinib (14)	II	Imatinib	20
Thalidomide—arm B (13)	Parallel phase II	Thalidomide alone	29
SAHA (15)	III	SAHA vs. placebo	3
ALD-518	I	Anti-IL-6 antibody	1
BMS-777607	I	MET tyrosine kinase inhibitor	1

Abbreviations: IL-6, interleukin 6; SAHA, suberoylanilide hydroxamic acid.

factors. Poor prognosis was defined by the presence of 3 or more of these factors (7).

Analysis in a subset of patients receiving thalidomide

Subgroup analysis was conducted on patients receiving thalidomide alone or in combination with chemotherapy as inflammatory markers and cytokines had been collected at baseline. The predictive values of WBC count, platelet count, NLR, mGPS, CRP, interleukin 6 (IL-6), IL-6-soluble receptor (IL-6 SR), and vascular endothelial growth factor (VEGF) were evaluated and possible interrelationships between these inflammatory markers, cytokines, and systemic symptoms were explored.

The mGPS is an inflammatory score based on blood levels of CRP and albumin. Baseline mGPS was recorded as follows: score 0 (CRP $\leq$ 10 mg/L and albumin $\geq$ 35 g/L); score 1 (CRP > 10 mg/L); score 2 (both CRP > 10 mg/L and albumin < 35g/L; ref. 22).

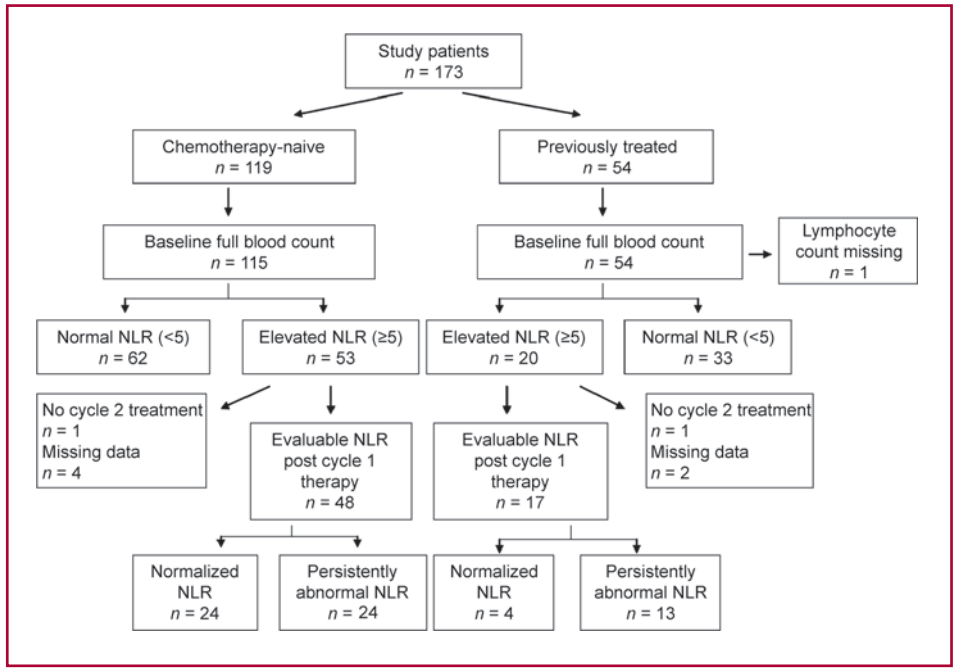

Fig. 1. Study flow chart. NLR, neutrophil-to-lymphocyte ratio.

The analysis of IL-6, IL-6 SR, and VEGF in the phase II thalidomide trial was carried out using the enzyme-linked immunosorbent assay method. As there is no defined cutoff value for these parameters, the median value was chosen *a priori* to categorize patients into high and low groups.

Statistical analysis

Overall survival was calculated from the date of commencement of systemic therapy and the date of death or last follow-up. Patients were censored at last follow-up if still alive or lost to follow-up. Survival curves were determined by the Kaplan–Meier method. Potential predictors of survival and treatment status (chemotherapy-naive vs. previously treated patients) were entered into univariate Kaplan–Meier models and compared with the log-rank test. Factors with a prognostic association in the univariate analysis were entered into a multivariate Cox regression model (forward sequential method) to determine their independent effect. Results of the Cox regression modeling are presented as hazard ratios (HR) and associated 95% confidence intervals (CIs). Variables with $P < 0.05$ were considered statistically significant. Separate analyses were carried out for chemotherapy-naive and previously treated patients. Pearson and Spearman correlations were used to examine the relationship between the inflammatory markers, cytokines, and systemic symptoms. The sensitivity and specificity of having a normal NLR in predicting 12-month survival in the chemotherapy-naive patients were calculated (excluding those who were censored before 12 months). All analyses were performed using the SPSS for Windows, Version 17.0.

Results

Patient demographics and outcomes

A total of 173 patients were included. One hundred nineteen patients participated in the first-line therapy protocols, whereas 54 patients had previous treatments. (Table 1). At the time of this report, 76% of patients were deceased. Among those who were still alive ($n = 42$), the median follow-up was 9.8 months (range, 0.8–82.1 months).

Baseline characteristics of the patient groups included in this study are given in Table 2. Full blood counts were unobtainable for 4 patients. Full clinical staging information was available only for 79 patients (all treated with first-line protocol): 9 patients with stage I–II and 70 patients with stage III–IV. Details for EORTC Prognosis Score were available for 102 patients (all treated with first-line protocol): 48 patients with a good risk and 54 patients with a poor risk.

Table 3 summarizes the patient characteristics at baseline according to NLR results (<5 vs. ≥5). Age, gender, performance status, hemoglobin difference, and clinical stage were not significantly different between the 2 groups. In contrast, epithelioid histologic subtype ($P = 0.017$), WBC count less than 8.3×10^9/L ($P < 0.001$), and platelet count 400×10^9/L or less ($P = 0.009$) were associated with a lower NLR value.

No patients showed clinical signs of sepsis or other inflammatory illnesses at the time of commencement of systemic therapy.

Prognostic role of NLR

The following variables were associated with better survival: female gender ($P = 0.044$), epithelioid histologic subtype ($P < 0.001$), baseline WBC count less than 8.3×10^9/L ($P = 0.008$), baseline platelet count 400×10^9/L or less ($P = 0.05$), and NLR less than 5 ($P < 0.001$), as well as chemotherapy-naive treatment status ($P = 0.019$). Multivariate analysis revealed that epithelioid subtype (HR = 2.0; 95% CI = 1.3–2.9; $P = 0.001$) and NLR less than 5 (HR = 2.7; 95% CI = 1.8–3.9; $P < 0.001$) were independent predictors of length of survival. The 1-year survival rate was 60% versus 26%, whereas the 2-year survival rate was 34% versus 10% for NLR less than 5 and 5 or greater, respectively.

Table 4 summarizes the univariate Kaplan–Meier and multivariate analysis for the number of factors examined and Figure 2A demonstrates the survival curves associated with normal and elevated NLRs for all patients (median OS: 16.7 vs. 6.6 months for NLR <5 and ≥5 respectively; $P < 0.001$).

In patients receiving first-line therapy, female gender (median OS: 15.2 vs. 10.6 months; $P = 0.027$), epithelioid histologic subtype (median OS: 16.7 vs. 5.8 months; $P < 0.001$), baseline WCC less than 8.3×10^9/L (median OS: 17.4 vs. 8.7 months; $P = 0.028$), NLR less than 5 (median OS: 19.2 vs. 6.6 months; $P < 0.001$), and a favorable EORTC prognosis score (median OS: 18.2 vs. 8.4 months; $P = 0.001$) were associated with better survival. Clinical stage was not associated with length of survival (median OS: 27.8 vs. 10.6 months for stages I–II and III–IV, respectively; $P = 0.219$). The sensitivity of having a normal NLR in predicting 12-months survival was 75% and the specificity was 61%. Only histologic epithelioid subtype (HR = 2.6; 95% CI = 1.5–4.5; $P < 0.001$) and NLR less than 5 (HR = 3.2; 95% CI = 1.9–5.2; $P < 0.001$) were predictive of length of survival in multivariate analysis. Figure 2B shows the survival curves according to NLR.

In patients receiving second- or third-line treatment, epithelioid histologic subtype and NLR less than 5 were associated with longer survival ($P = 0.047$ and 0.025, respectively). In multivariate analysis, only NLR less than 5 (HR = 2.1; 95% CI = 1.1–3.9; $P = 0.028$) was an independent predictor of length of survival. Figure 2C shows the survival curves according to NLR in the previously treated group (median OS: 10.4 vs. 3.8 months for NLR <5 and ≥5 respectively; $P = 0.025$).

Normalization of NLR after 1 cycle of systemic therapy (subgroup analysis)

A total of 65 patients were included in this subgroup analysis. (Fig. 1) Twenty-eight patients (43%) showed a

Table 2. Baseline characteristics for the study patients

Variables	All patients ($N = 173$)		Chemotherapy-naive group ($n = 119$)		Previously treated group ($n = 54$)	
	N	%	*n*	%	*n*	%
Median age, y	61.5		61		63.5	
Range	36–82		41–82		36–79	
Gender						
Male	141	82	98	82	43	80
Female	32	18	21	18	11	20
Performance status						
0	36	21	31	26	5	9
1	106	61	69	58	37	69
2	22	13	14	12	8	15
3	2	1	1	1	1	2
Missing	7	4	4	3	3	5
Histologic subtype						
Epithelioid	110	64	82	69	28	52
Biphasic	26	15	13	11	13	24
Sarcomatoid	12	7	10	8	2	4
Others	11	6	5	4	6	11
Unspecified	14	8	9	8	5	9
Baseline white blood cell count ($\times 10^9$/L)						
<8.3	78	45	53	46	25	46
≥8.3	91	53	62	52	29	54
Baseline platelet counts ($\times 10^9$/L)						
≤400	95	55	61	51	34	63
>400	74	43	54	45	20	37
Hemoglobin difference (g/L)						
<10	39	23	26	22	13	24
≥10	130	75	89	75	41	76
Neutrophil-to-lymphocyte ratio						
<5	95	55	62	52	33	61
≥5	73	42	53	46	20	37
Median overall survival, mo	10.6		11.7		8.0	
	95% CI = 9.0–12.1		95% CI = 7.6–15.8		95% CI = 3.8–12.2	

Abbreviations: CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer.

normalization of NLR after 1 cycle of systemic therapy. Figure 2D shows that a normalization of NLR was associated with longer survival compared with patients with persistently abnormal NLR (median OS: 7.8 vs. 5.0 months for patients with normalized NLR and persistently abnormal NLR, respectively; $P = 0.034$).

Subgroup analyses in patients receiving thalidomide

Inflammatory markers at baseline. In patients receiving thalidomide alone or in combination with chemotherapy, NLR (median OS: 14.2 vs. 6.6 months for NLR <5 and ≥5, respectively; $P = 0.015$) and CRP (median OS: 14.3 vs. 6.8 months for CRP <20 and ≥20 respectively; $P = 0.03$) were significant inflammatory prognostic markers in univariate analysis, whereas total WBC count, platelet count, IL-6, IL-6 SR, mGPS, and VEGF were not. NLR remained significant in multivariate analysis (HR = 2.3; 95% CI = 1.3–4.3; $P = 0.007$).

Symptoms, cytokines, and NLR. An exploratory analysis in 63 thalidomide patients suggested that NLR is not associated with IL-6, IL-6 SR, and VEGF. NLR was correlated with WBC count and CRP, with the Pearson correlation ρ of 0.581 ($P < 0.001$) and 0.438 ($P = 0.001$), respectively. The clinical symptom of weight loss was associated with increased baseline NLR ($\rho = 0.37$, $P = 0.021$).

Discussion

The results from this study confirm our hypothesis and suggest that an elevated NLR is an independent predictor for poor survival in MM patients undergoing systemic therapy regardless of whether this is given as an

Table 3. Baseline characteristics based on NLR groups for all study patients

Baseline characteristics	NLR ratio				*P*
	<5 (*n* = 95)		≥5 (*n* = 73)		
	n	%	*n*	%	
Age					
<65	57	60	38	52	0.303
≥65	38	40	35	48	
Gender					
Male	76	80	61	84	0.555
Female	19	20	12	16	
Performance status					
ECOG 0	21	23	14	20	0.606
ECOG ≥1	70	77	57	80	
Histologic subtype					
Epithelioid	65	76	41	59	0.017
Nonepithelioid	20	24	29	41	
Baseline white cell count ($\times 10^9$/L)					
<8.3	59	62	19	26	<0.001
≥8.3	36	38	54	74	
Baseline platelet count ($\times 10^9$/L)					
≤400	62	65	33	45	0.009
>400	33	35	40	55	
Hemoglobin difference, g/L					
<10	24	25	15	21	0.473
≥10	71	75	58	79	
Clinical stage					
I–II	6	16	3	8	0.269
III–IV	32	84	36	92	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NLR, neutrophil-to-lymphocyte ratio.

initial or subsequent therapy. This result is in accordance with previous observations on the association between NLR and a variety of cancers such as lung cancer, colorectal cancer, and resected intrahepatic cholangiocarcinoma (17–20, 23). In our current retrospective series of MM patients, NLR could stratify patient groups, with a survival difference of 10 months (16.7 vs. 6.6 months).

The baseline characteristics of patients receiving first-line therapy were comparable with the largest phase III trial in MM in terms of median age, gender distribution, good performance status, and epithelioid histologic subtype (4). The survival outcome was similar to that seen in the large phase III trial (4). Thus, although this was a retrospectively collected group, it seems typical of patients with mesothelioma receiving chemotherapy. In the first-line setting, we found a survival difference of 12.6 months between the NLR groups (19.2 vs. 6.6 months). This degree of survival difference stratified by a simple blood test is clinically significant. Furthermore, 75% of patients in the first-line setting with a normal NLR had a survival of 12 months or greater and 61% of patients with an elevated NLR lived for less than 12 months.

Inflammation seems to be closely associated with prognosis in patients with MM, and it seems that NLR is also related to other indices of inflammation such as WBC count and CRP. We did not find an association between NLR and baseline IL-6, IL-6 SR, or VEGF. This may indicate that a number of proinflammatory factors are determining the NLR rather than an individual cytokine. It is likely that there is a complex interaction of proinflammatory and anti-inflammatory proteins.

It is conceivable that patients with more advanced disease at the time of diagnosis may have more exaggerated systemic inflammatory response and therefore higher NLR. In our series, there was a trend for patients with higher clinical stage to be associated with elevated NLR; however, this did not reach statistical significance. This may, in part, be due to the difficulties of stage classification in MM as well as the limited sample size.

Importantly, NLR emerged as the best inflammatory marker to predict survival from the exploratory analysis of the various cytokines and inflammatory markers. Unless further studies are available to suggest its predictive roles in therapy in MM, the high cost, limited availability, and absence of standardization argue against the routine

Table 4. Univariate and multivariate analyses of the factors predictive of overall survival in all patients ($N = 173$)

Variable	Univariate Analysis					Multivariate analysis		
	n	No. of deaths	Median survival, mo	95% CI	*P*	HR	95% CI	*P*
Age, y								
<65	98	71	10.7	8.7–12.6	0.238			
≥65	75	60	10.4	6.7–14.1				
Gender								
Male	141	108	9.8	8.1–11.6	0.044		Not significant	
Female	32	23	15.2	8.5–21.9				
Performance status								
ECOG 0	36	26	16.2	11.6–20.8	0.227			
ECOG ≥1	130	99	9.7	8.1–11.2				
Histologic subtype								
Epithelioid	110	80	15.2	11.3–19.1	<0.001	2.0	1.3–2.9	0.001
Nonepithelioid	49	40	5.8	4.5–7.1				
Baseline white cell count ($\times 10^9$/L)								
<8.3	78	59	15.2	9.2–21.3	0.008		Not significant	
≥8.3	91	71	8.6	7.4–9.8				
Baseline platelet count ($\times 10^9$/L)								
≤400	95	75	11.5	8.3–14.7	0.05		Not significant	
>400	74	55	8.4	5.6–11.3				
Hemoglobin difference, g/L								
<10	39	33	15.2	9.5–20.9	0.185			
≥10	130	97	9.7	8.1–11.3				
Neutrophil-to-lymphocyte ratio								
<5	95	67	16.7	10.6–22.8	<0.001	2.7	1.8–3.9	<0.001
≥5	73	62	6.6	4.4–8.8				
Treatment status								
Chemotherapy-naive	119	85	11.7	7.6–15.8	0.019		Not significant	
Previously treated	54	46	8.0	3.8–12.2				

Abbreviation: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

measurement of plasma cytokines and their receptors (e.g., IL-6, IL-6 SR, and VEGF) in clinical practice. In comparison, the NRL is a relatively inexpensive test and can readily be incorporated into routine clinical practice.

Patients whose NLR normalized after 1 cycle of systemic therapy were found to have significantly longer survival than those whose NLR remained abnormal with a survival difference of 2.8 months ($P = 0.034$). This finding confirms the important role of NLR in predicting survival and provides an early marker both to predict outcome in MM patients with an initial abnormal NLR and to assist clinical decision making.

We acknowledge that our findings require validation by using an independent series of patients with standardized treatment, although such cohorts may be difficult to access and chemotherapy studies have previously not routinely collected lymphocyte counts.

Our study results support that inflammatory processes may be appropriate targets for interventions aimed at improving survival in this highly symptomatic condition. Given the prevalence of the elevated NLR in MM and its associated poor prognosis, one could think of evaluating the efficacy of specific (antibodies to TNF-α and IL-6) and nonspecific anti-inflammatory interventions in an attempt to improve outcomes.

Some studies have suggested that tumor stage is an important prognostic factor in MM (6, 16, 24). In our series, clinical stage was not a positive predictor for prognosis. This may be attributed to the substantial amount of missing staging data and a consequent small number of patients with early stage disease ($n = 6$). We also examined the EORTC prognostic scoring system. Our results confirmed that the EORTC score provides useful prognostic information, but in multivariate analysis, the

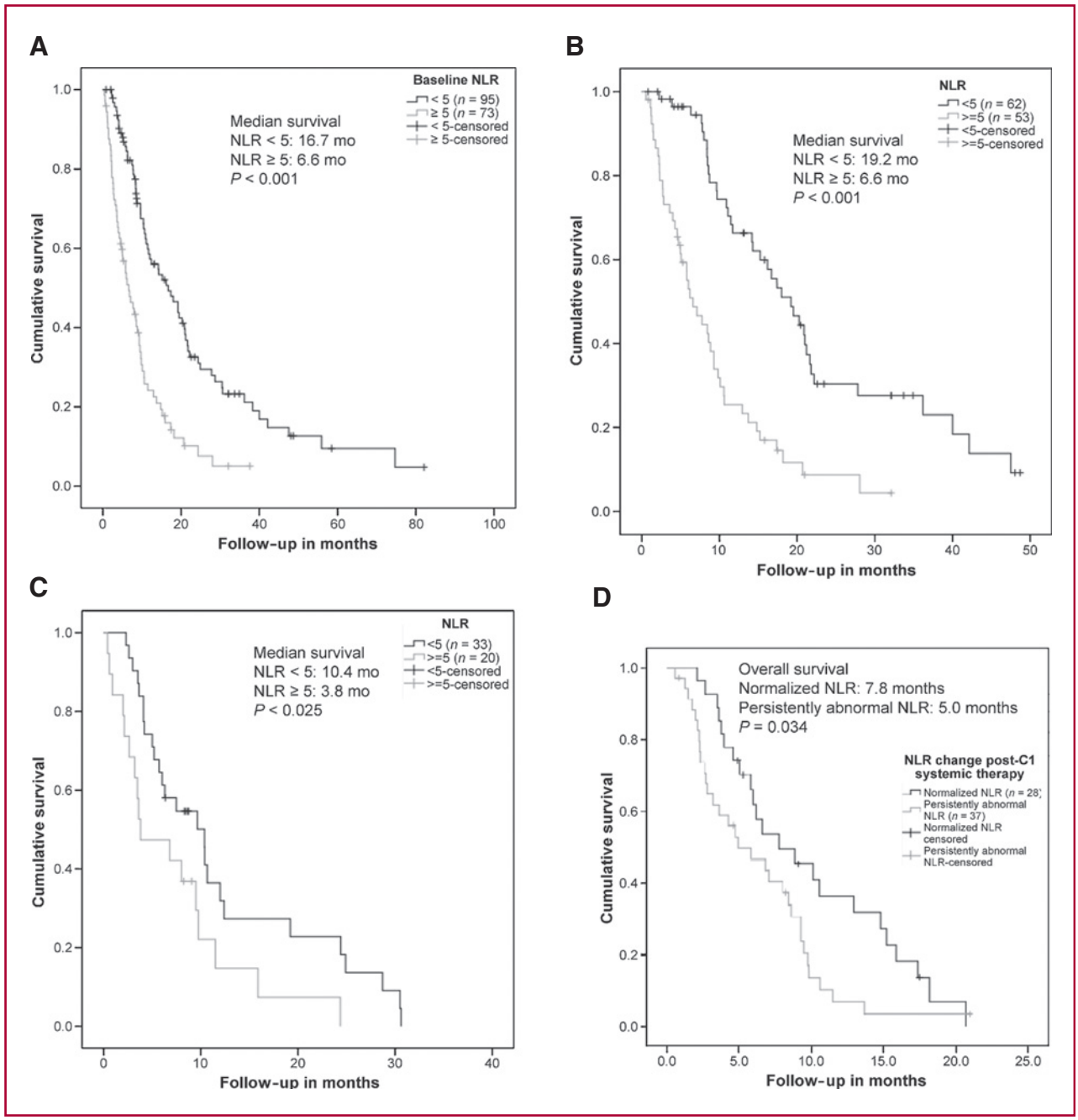

Fig. 2. Kaplan–Meier curves of NLR for A, all patients; B, chemotherapy-naive group; C, previously treated group; D. Kaplan–Meier curves for normalization of NLR in all patients.

EORTC prognostic score did not remain an independent prognostic factor.

One other limitation of our study was the inability to include the CALGB prognostic score as a prognostic variable due to incomplete clinical information (i.e., clinical symptoms of weight loss and chest pain). As such, the prognostic role of NLR could not be directly compared with this prognostic index. Such correlations should be undertaken in future analyses.

In conclusion, we found that an NLR less than 5 was an independent predictor of longer survival for patients with MM undergoing systemic therapy. MM patients have a survival benefit of 10.1 months if their NLR is less than 5 (16.7 vs. 6.6 months). NLR is in a good position to become a clinically useful marker, given its high prevalence and prognostic importance of an elevated NLR. The low cost and easy accessibility and reproducibility of a full blood count are other features promoting its use in clinical practice.

Disclosure of Potential Conflicts of Interest

Dr. N. Pavlakis is on an advisory board with Lilly and has received a travel grant and speaking honoraria from Lilly.

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