

Keywords: inflammation; NSCLC; NLR; PLR; mGPS; survival

# Prognostic performance of inflammation-based prognostic indices in primary operable non-small cell lung cancer

D J Pinato<sup>1</sup>, R J Shiner<sup>2</sup>, M J Seckl<sup>3</sup>, J Stebbing<sup>3</sup>, R Sharma<sup>1</sup> and F A Mauri<sup>\*4</sup>

<sup>1</sup>Division of Experimental Medicine, Hammersmith Campus of Imperial College London, Du Cane Road, W120HS London, UK;

<sup>2</sup>Department of Respiratory Medicine, National Heart and Lung Institute, Hammersmith Hospital, Du Cane Road, W120HS London, UK; <sup>3</sup>Division of Oncology, Hammersmith Campus of Imperial College London, Du Cane Road, W120HS London, UK and

<sup>4</sup>Department of Pathology, Hammersmith Campus of Imperial College London, Du Cane Road, W120HS London, UK

**Background:** At least 30% of patients with primary resectable non-small cell lung cancer (NSCLC) will experience a relapse in their disease within 5 years following definitive treatment. Clinicopathological predictors have proved to be suboptimal in identifying high-risk patients. We aimed to establish whether inflammation-based scores offer an improved prognostic ability in terms of estimating overall (OS) and recurrence-free survival (RFS) in a cohort of operable, early-stage NSCLC patients.

**Methods:** Clinicopathological, demographic and treatment data were collected prospectively for 220 patients operated for primary NSCLC at the Hammersmith Hospital from 2004 to 2011. Pretreatment modified Glasgow Prognostic Score (mGPS), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were tested together with established prognostic factors in uni- and multivariate Cox regression analyses of OS and RFS.

**Results:** Half of the patients were male, with a median age of 65. A total of 57% were classified as stage I with adenocarcinoma being the most prevalent subtype (60%). Univariate analyses of survival revealed stage ( $P < 0.001$ ), grade ( $P = 0.02$ ), lymphovascular (LVI,  $P = 0.001$ ), visceral pleural invasion (VPI,  $P = 0.003$ ), mGPS ( $P = 0.02$ ) and NLR ( $P = 0.04$ ) as predictors of OS, with stage ( $P < 0.001$ ), VPI ( $P = 0.02$ ) and NLR ( $P = 0.002$ ) being confirmed as independent prognostic factors on multivariate analyses. Patients with more advanced stage ( $P < 0.001$ ) and LVI ( $P = 0.008$ ) had significantly shorter RFS.

**Conclusions:** An elevated NLR identifies operable NSCLC patients with a poor prognostic outlook and an OS difference of almost 2 years compared to those with a normal score at diagnosis. Our study validates the clinical utility of the NLR in early-stage NSCLC.

Non-small cell lung cancer (NSCLC) accounts for 80% of primary bronchogenic carcinomas (Govindan *et al*, 2006) and leads the ranking of cancer-related mortality in the western world (Siegel *et al*, 2012). The prognosis of NSCLC is however stage dependent and only patients who present with early-stage disease, adequate pulmonary reserve and preserved performance status are candidates for resection, with 5-year survival rates ranging from 70% to 80% (Sakurai *et al*, 2010) in stage IA to only 30% in stage IIIA (Goya *et al*, 2005) disease. Recently, increasing research efforts

have been directed towards the identification of clinical, pathological and biologic factors that can identify the 30% of patients with early-stage disease who will experience tumour recurrence despite adequate radical treatment. As recurrence is a major determinant of patient mortality, the prospect of predicting disease relapse at presentation might result in an improved treatment allocation such that patients at high risk of recurrence may be offered adjuvant therapies following radical surgery. In this context, previous studies have identified clinicopathological features such as larger tumour

\*Correspondence: Dr FA Mauri; E-mail: f.mauri@imperial.ac.uk

Received 12 December 2013; revised 11 February 2014; accepted 24 February 2014; published online 25 March 2014

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size, the presence of lymphovascular (LVI) (Lopez Guerra *et al*, 2013) or visceral pleural invasion (VPI) (Fibla *et al*, 2012) as adverse prognostic traits in early-stage NSCLC. However, conflicting results emerging from independent studies have cast doubts upon the reliability of these prognostic factors (Hung *et al*, 2007). More recent studies have focussed on the differential protein expression profile discriminating recurrent from non-recurrent NSCLC. For example, a distinct upregulation of the mammalian target of rapamycin (m-TOR) has emerged as a peculiar trait associated with disease recurrence in independent cohorts (Dhillon *et al*, 2010; Gately *et al*, 2012).

Systemic inflammation represents an area of growing interest in the management and prognostic assessment of solid tumours. It has been shown that most of the systemic symptoms relating to the presence of cancer including weight loss, anorexia, cachexia and anaemia are inflammatory driven and result from a condition of systemic cytokine excess that can be either triggered by the tumour itself or as part of the host's innate response against cancer (Moore *et al*, 2010).

A subclinical inflammatory diathesis associated with hypoalbuminaemia, raised C-reactive protein (CRP) and derangements in the full blood count such as lymphopenia combined with reactive neutrophilia and thrombocytosis, are known independent prognostic factors for a wide variety of solid tumours (McMillan, 2012). Prognostic indices based on such laboratory parameters, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and the modified Glasgow Prognostic Score (mGPS), which combines hypoalbuminaemia and elevated CRP in a 3-tiered prognostic model, have emerged as objective, inexpensive and stage-independent predictors of survival in cancer (Proctor *et al*, 2011).

There is mounting evidence supporting a prognostic role for the NLR (Yao *et al*, 2012), PLR (Arrieta *et al*, 2010) and mGPS (Forrest *et al*, 2005) in NSCLC. However, most of the studies have focussed on inoperable NSCLC a patient subgroup where cancer cachexia and poor performance status are far more prevalent than in early-stage disease (Forrest *et al*, 2004, 2005; Giannousi *et al*, 2012). Moreover, studies investigating the prognostic impact of systemic inflammation in early NSCLC were conducted in Asian populations (Tomita *et al*, 2011, 2012), where inherent differences exist in terms of molecular features (Sequist *et al*, 2007) and survival outcomes compared with western populations (Ou *et al*, 2009). Following on from our previous experience in hepatocellular carcinoma, where we validated a new inflammation-based index as a stage-independent predictor of survival (Pinato *et al*, 2012c); here, we have evaluated and compared the prognostic value of a panel inflammatory biomarkers such as NLR, PLR and mGPS in a western population with resectable NSCLC.

## MATERIALS AND METHODS

**Patient population.** A series of 220 consecutive patients who underwent surgical treatment for primary NSCLC at Imperial College NHS Trust from 2004 to 2011 were included in a prospectively maintained database. Patients with evidence of an ongoing systemic inflammatory reaction (i.e., active infection or the presence of chronic inflammatory conditions) were excluded. Histological subclassification, grade, pathological stage according to the TNM Classification (7th edition) (Sobin *et al*, 2009) and the presence of adverse features such as lymphovascular, pleural invasion or evidence of residual tumour at the resection margin were confirmed following archival haematoxylin and eosin slides review by a consultant histopathologist with expertise in lung pathology (FM). Complete clinical and follow-up information including patient's demographics, performance status and

complete preoperative blood picture were recorded. Tumour recurrence during routine post-surgical follow-up was recorded. Overall (OS) and recurrence-free survival (RFS) times were calculated from the time of surgery. Inflammation-based prognostic scores were calculated on preoperative blood tests as previously described (Pinato *et al*, 2012c). Platelet-to-lymphocyte ratio and NLR were derived by respectively dividing either platelet or neutrophil absolute counts with the total lymphocyte count. A resulting ratio of  $>300$  was used to define an elevated PLR whereas a cutoff point of  $>5$  was used to define an elevated NLR in keeping with the previously published literature (Pinato *et al*, 2012a). The mGPS was computed based on serum albumin and CRP levels. Briefly, patients with both normal albumin ( $>35\text{ g l}^{-1}$ ) and CRP ( $<10\text{ mg l}^{-1}$ ) concentrations were scored as 0. Patients in whom only one of these abnormalities was present were allocated a score of 1, while those with both abnormal CRP and albumin were given a score of 2. The study was approved by the local Ethical Committee and conducted in accordance with the principles of the Declaration of Helsinki.

**Statistical analysis.** The presence of significant associations between clinico-pathological variables was determined by means of Chi-square or Fisher's exact test as appropriate. Kaplan-Meier statistics and log-rank test were used to study the impact of the different clinical factors associated with OS and RFS on univariate analysis, with significant variables ( $P<0.05$ ) being further tested on a multivariate stepwise backward Cox regression model to validate their independent prognostic value. Variables with a  $P$ -value of greater than 0.10 were removed from the model. A  $P$ -value of  $<0.05$  was taken to be significant. All statistical analysis was conducted using SPSS statistical package 19.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

**Clinicopathologic profile of patients.** The baseline patient characteristics are shown in Table 1. A total of 220 subjects were identified, 50% males with a median age of 65 years. All patients had a Karnofsky performance status of  $\geq 90$  and adequate pulmonary reserve with FEV<sub>1</sub> values  $>1.5\text{ l}$  assessed before surgery. Primary lung adenocarcinoma was the most prevalent histotype (60%) followed by squamous cell carcinoma (24%). Pathological examination revealed 57% of the patients being classified as stage I. Lymphatic diffusion to N1 nodes was present in 17% of the patients, while 6% had positive N2 nodes. N3 diffusion was found in 1% of the patients. According to clinical criteria, a total of 15 patients received adjuvant radiotherapy following radical surgery, while systemic chemotherapy was administered in 16 subjects. Combined adjuvant chemoradiotherapy was initiated in eight subjects. The most commonly prescribed chemotherapy regimen was three-weekly carboplatin AUC 5 and gemcitabine  $1000\text{ mg m}^{-2}$  days 1 and 8 of each 21-day cycle for 4 cycles (50%), followed by cisplatin-based regimens either in combination with gemcitabine (25%) or pemetrexed (25%).

On the basis of the preoperative complete blood picture, 65 patients (32%) were hypoalbuminaemic (median  $37\text{ g l}^{-1}$ , range  $19\text{--}50\text{ g l}^{-1}$ ) while 66 (31%) had a CRP of  $>10\text{ mg l}^{-1}$  (median 5, range  $0\text{--}229\text{ mg l}^{-1}$ ). The mGPS could be reconstructed in 200 patients due to missing preoperative CRP ( $n=8$ ) or albumin values ( $n=12$ ). An abnormal mGPS (score 1–2) was found in 68 patients (31%). An NLR of  $>5$  was found in 21 patients (10%), while only 8 patients (3%) had a PLR of  $>300$ . Patients with advanced mGPS were more likely to have Hb values  $<12$  ( $P<0.001$ ), less differentiated tumours ( $P=0.006$ ) with a higher proportion of pleural invasion ( $P=0.03$ ). Patients with an elevated

Table 1. General characteristics of the patient population

Baseline characteristic	n = 220 (%)
<b>Gender</b>	
Male	110 (50)
Female	110 (50)
<b>Age, years</b>	
<65	115 (53)
≥65	105 (47)
<b>Tumour size, cm</b>	
<5.0	187 (85)
≥5.0	33 (15)
<b>pTNM stage</b>	
Ia	76 (34)
Ib	50 (23)
IIa	45 (21)
IIb	20 (9)
IIIa	29 (13)
<b>Tumour grade</b>	
Well differentiated	43 (20)
Moderately differentiated	110 (50)
Poorly differentiated	67 (30)
<b>Histological subtype</b>	
Adenocarcinoma	132 (60)
Squamous cell carcinoma	53 (24)
Adeno-squamous carcinoma	8 (4)
Typical carcinoid	14 (6)
Pleomorphic carcinoma	6 (3)
Large cell lung carcinoma	3 (1)
Undifferentiated carcinoma	4 (2)
<b>Lymphovascular invasion</b>	
Absent	120 (56)
Present	100 (44)
<b>Pleural invasion</b>	
Absent	176 (80)
Present	44 (20)
<b>Resection margins</b>	
Clear	189 (86)
Involved	31 (14)
<b>Surgical treatment</b>	
Wedge resection	51 (23)
Lobectomy	158 (71)
Bi-lobectomy	11 (6)
<b>Albumin, g l<sup>-1</sup></b>	
>35	140 (68)
<35	65 (32)
<b>Haemoglobin, g dl<sup>-1</sup></b>	
>12.0	165 (75)
<12.0	55 (25)
<b>White cell count, 10<sup>9</sup> l<sup>-1</sup></b>	
<11.0	198 (90)
>11.0	22 (10)

NLR were more likely to be anaemic ( $P=0.02$ ). Among patients with an NLR of  $>5$  at diagnosis, a total of two patients received adjuvant treatments consisting of four cycles of cisplatin/etoposide chemotherapy in one case and post-operative radiation therapy in the second.

**Inflammation-based indices and survival.** At the end of observation (September 2012), 51 patients (23%) had documented evidence of disease relapse and 61 had died (28%). The median OS of the entire cohort was 13 months (range 1–87 months) while the median RFS was 11 months (range 1–87 months). In total, 114 patients (52%) had a documented follow-up period extending beyond 12 months from diagnosis.

Univariate analyses revealed pTNM stage ( $<0.001$ ), tumour grade ( $P=0.01$ ), the presence of lymphovascular ( $P=0.001$ ), pleural invasion ( $P=0.003$ ), NLR  $>5$  ( $P=0.04$ , Figure 1A) and advanced mGPS ( $P=0.02$ , Figure 1B) as significant predictors of OS. Multivariate analysis confirmed pTNM stage ( $P<0.001$ ), the presence of pleural invasion ( $P=0.02$ ) and NLR  $>5$  ( $P=0.002$ ) as independent risk factors predicting patients' mortality (Table 2). Patients in whom the NLR was  $>5$  had a median OS of 22 months (95% confidence interval (CI) 15–29 months) while patients with NLR  $<5$  had a median OS value of 45 months (95% CI 36–54 months). When stratified according to the mGPS, median OS was 50 months for mGPS 0 (95% CI 37–62 months), 23 months for mGPS 1 (95% CI 10–36 months) and 44 months for mGPS 2 (95% CI 6.8–81). Neither mGPS ( $P=0.21$ ), NLR ( $P=0.63$ ) nor PLR ( $P=0.54$ ) predicted shorter RFS after surgery. Significant predictors of tumour relapse included pTNM stage ( $P<0.001$ ) and the presence of LVI ( $P=0.008$ ).

## DISCUSSION

The connection between inflammation and cancer dates back to the origin of cellular pathology itself, when Rudolf Virchow first hypothesised a pathogenic role for the immune infiltrate commonly found adjacent to most neoplastic tissues (Balkwill and Mantovani, 2001). After almost two centuries, mechanistic studies have provided solid evidence to support the pathogenic and prognostic importance of a pro-inflammatory tumour microenvironment, which is currently considered as a hallmark of cancer progression (Hanahan and Weinberg, 2011).

Chronic inflammation predates the clinical onset of NSCLC (O'Callaghan *et al*, 2010) and the biochemical 'cross-talk' between inflammatory cells and the growing neoplastic clone can influence tumour cell survival acting on immune-evasion systems and by enhancing angiogenesis (Bremnes *et al*, 2011). The systemic effects of cancer-related inflammation can be easily quantified using routinely available blood parameters such as NLR, PLR and mGPS, all of which have been explored as prognostic traits in NSCLC (Forrest *et al*, 2005; Arrieta *et al*, 2010; Tomita *et al*, 2012).

In our study, we assessed all three parameters to evaluate whether the presence of a subclinical systemic inflammatory reaction before definitive treatment could better identify patients who would have inferior survival outcomes after surgery. Strikingly, we found that the NLR was the only inflammation-based score with independent prognostic prediction on OS.

In our study, the first to explore the prognostic performance of the mGPS in early-stage NSCLC, the score demonstrated suboptimal discriminatory ability, with patients grouped as being of intermediate risk (i.e., mGPS 1) not differing significantly from patients of poor risk (i.e., mGPS 2) in terms of OS. A number of studies have confirmed the mGPS as a valuable and objective tool to assess patient's prognosis in advanced NSCLC (Forrest *et al*, 2005; Giannousi *et al*, 2012; Leung *et al*, 2012), with non-inferior accuracy to that of more established predictors such as

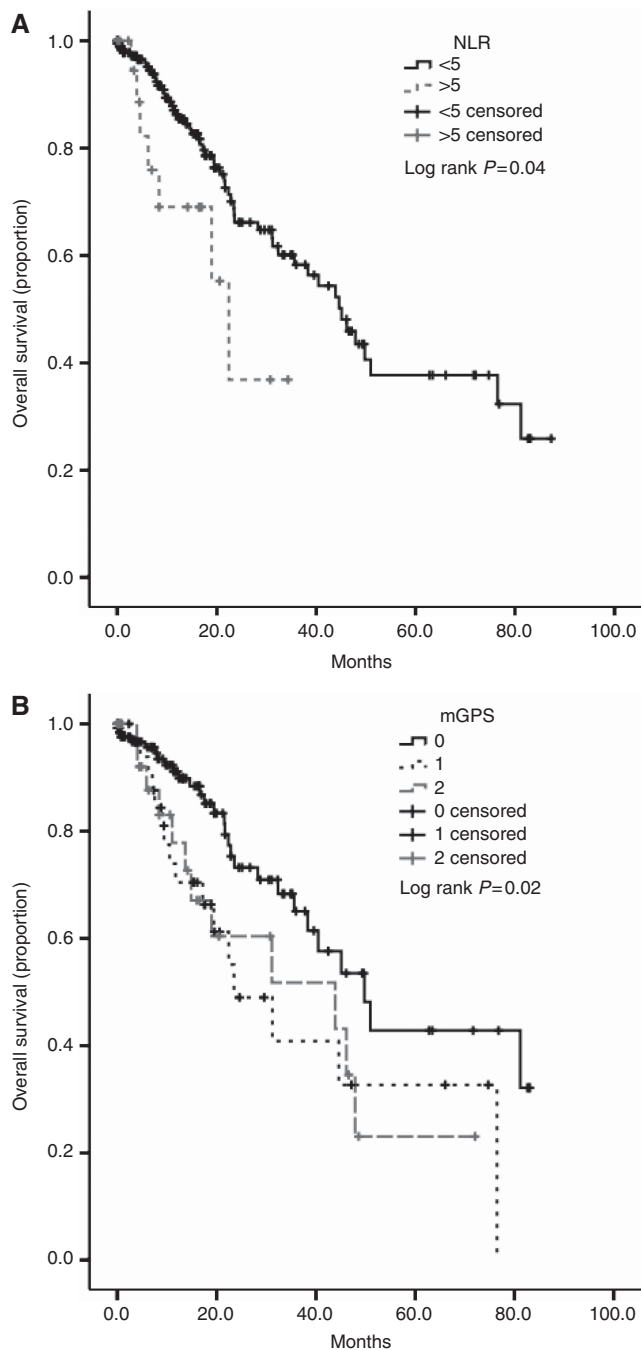


Figure 1. Kaplan–Meier curve analysis showing the difference in median OS for patients with primary operable NSCLC categorised according to their pretreatment NLR (A) and mGPS, where patients are categorised in low, intermediate or poor risk (mGPS of 0, 1 and 2, respectively) (B).

performance status (Forrest *et al*, 2004). However, the lack of reproducibility that we found seems to suggest that the mGPS is a stage-dependent prognostic factor in NSCLC, as a likely result of worsening cachexia in advanced tumours, that is associated with hypoalbuminaemia and elevated CRP (Wallengren *et al*, 2013). The same is not true for the NLR, whose prognostic power is apparent in both localised (Tomita *et al*, 2011, 2012) and metastatic cases of NSCLC (Cedres *et al*, 2012; Yao *et al*, 2012).

In our study, the first to validate the NLR as a prognostic marker in early-stage NSCLC, we confirmed that an elevated NLR identifies patients with a poor prognostic outlook and a survival

Table 2. Clinicopathological predictors of overall survival					
Variable	N = 220	Overall survival			
		Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
<b>pTNM stage</b>					
I/II/III	126/65/29	1.4 (1.2–1.6)	<0.001*	1.4 (1.2–1.7)	<0.001*
<b>Grade</b>					
Good/Moderate/Poor	43/110/67	1.6 (1.1–2.3)	0.02*		
<b>Lymphovascular invasion</b>					
Absent/Present	120/100	2.5 (1.4–4.3)	0.001*		
<b>Pleural invasion</b>					
Absent/Present	176/44	2.3 (1.3–4.1)	0.003*	2.2 (1.2–3.9)	0.02*
<b>Resection margin</b>					
Clear/involved	189/31	0.8 (0.4–1.7)	0.64		
<b>NLR</b>					
<5/>5	198/21	2.3 (1.0–5.0)	0.04*	3.8 (1.6–8.9)	0.002*
<b>PLR</b>					
<300/>300	211/8	1.6 (0.6–5.6)	0.32		
<b>mGPS</b>					
0/1/2	131/39/29	1.5 (1.0–2.0)	0.02*		

Abbreviations: CI = confidence interval; mGPS = modified Glasgow Prognostic Score; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; pTNM = Pathological Tumour Node Metastasis stage according to the 7th Edition of the TNM Classification. Associations reaching statistical significance ( $P < 0.05$ ) are marked with an asterisk (\*).

difference of almost 2 years compared to those with a normal score at diagnosis. Interestingly, such an effect on patient survival is independent of the tumour stage or other adverse pathological features including grade, LVI or VPI. Our results that confirm the accuracy of NLR as a prognostic predictor in early-stage NSCLC in a western patient group are consistent with the results obtained from an Asian population of 284 consecutive patients also with early-stage NSCLC (Tomita *et al*, 2011). This similarity in the findings comes despite the fact that the distribution of risk factors, pathogenic molecular alterations and clinical outcome are notably different in an Asian patient group.

In our comparative analysis of prognostic scores, we also tested the PLR, whose role in predicting patient’s survival had not been taken into consideration before in NSCLC. In our study, only a limited fraction of patients had an elevated PLR, with no significant impact on survival. An abnormal PLR has been previously noted to associate with increased risk of grade III/IV toxicity from systemic treatment in advanced NSCLC (Arrieta *et al*, 2010). Whether the PLR may have any prognostic role in inoperable tumours remains to be ascertained.



This is not the first study to support the prognostic validity of the systemic inflammatory response in cancer. In a previous study involving >12 000 patients, the NLR was found as a significant and accurate predictor of cancer-specific survival, independently of histotype and stage (Proctor *et al*, 2012). This observation follows growing evidence from a number of smaller, mostly single institution-based studies, which independently confirmed a prognostic role for inflammation-based indices in thoracic (Pinato *et al*, 2012a), gastrointestinal (Sharma *et al*, 2008b; Pinato *et al*, 2012b, 2012c; Wang *et al*, 2012), genitourinary malignancies (Hilmy *et al*, 2006; Ramsey *et al*, 2007) as well as in many others (Hilmy *et al*, 2006; Sharma *et al*, 2008a; Mohamed *et al*, 2014; Pinato *et al*, 2014). More recent evidence has shown that resolution of the systemic inflammatory response may reflect disease-modulating effects from locoregional and systemic anticancer therapies and predict for survival benefit from treatment (Kao *et al*, 2010; Chua *et al*, 2012; Pinato and Sharma, 2012).

The biological grounds justifying a prognostic role for systemic inflammation are however yet to be fully elucidated. It is well established that the symptomatic burden that is typically associated with progressive malignant disease specifically anorexia, weight loss, muscle wasting and adipose tissue depletion are part of a complex paraneoplastic derangement in metabolism driven by the excessive secretion of pro-inflammatory cytokines such as interleukin (IL) 6 (Batista *et al*, 2013), IL-8 and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) (Esper and Harb, 2005). Some of these mediators such as IL-6 retain direct antiapoptotic as well as pro-angiogenic effects, conferring survival advantage to proliferating tumour cells and promoting resistance to cytotoxic therapies (Guo *et al*, 2012). Moreover, the effects of pro-inflammatory cytokine excess, whether directly produced by the tumour or as part of the host's innate response, can exert immunomodulatory effects by suppressing specific antitumour immune mechanisms (Elkord *et al*, 2010). T-cell function impairment, often paralleled by relative lymphopenia in the full blood count, is at least in part responsible for an increase in the NLR (Ray-Coquard *et al*, 2009).

To conclude, our study has validated the NLR as the only inflammation-based prognostic score in operable NSCLC. Interestingly, our study confirms TNM stage and VPI as predictors of OS, while stage and LVI emerged as risk factors for shortened time to relapse. Given the prospective nature of our study that included unselected consecutive referrals, the significant proportion of patients with <12 months follow-up, amounting to 48%, should be acknowledged as a limitation to our survival analysis, warranting independent validation of our findings in a separate data set. However, the level of statistical significance achieved for the prognostic traits tested in our series leaves little doubt about the reliability and reproducibility of our findings. The NLR is a proven objective, reproducible and inexpensive predictor of survival in both operable and advanced stage NSCLC and consideration should be given for its routine clinical use.

## ACKNOWLEDGEMENTS

MJS is supported by the Imperial College Experimental Cancer Medicine Centre and Imperial NIHR Biomedical Research Centre grants. The funding sources did not have any role in study design, data collection and analysis, decision to publish.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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