Background
Lung cancer causes the most cancer-related deaths worldwide. Increasing knowledge of tumour biology and multimodal treatments have helped improve treatment, and several prognostic factors exist, but overall survival remains poor, except in stage I, for which survival ranges between 60 and 80% [1, 2].

Prognostic factors related not to the tumour itself but to the patient’s general health status have been studied, including nutritional status and inflammatory status. Nutritional status is a prognostic factor in patients with lung cancer [3, 4], and our group has confirmed that nutritional status affects survival and postoperative outcomes in patients with lung cancer who undergo surgical resection [5].

Another prognostic factor that has been associated with survival and complications is inflammatory status. Multiple parameters can be used to determine the inflammatory status of a patient with cancer, but blood
markers that are often used in preoperative assessment due to being simple to obtain are C reactive protein, absolute values of neutrophils, lymphocytes, monocytes and platelets, and the ratios of neutrophils to lymphocytes, platelets to lymphocytes and lymphocytes to monocytes. Certain levels of these parameters are associated with better or worse survival in various cancers, including lung cancer [6, 7].

The European Lung Cancer Working Group confirmed that patients with a high neutrophil count had worse survival [8]. Likewise, a high neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are markers of worse prognosis in patients with cancer in general and particularly in lung cancer [9, 10]; however, within the inflammatory response, lymphocytes and monocytes both play an important role in postoperative outcomes following lung cancer resection [11, 12].

In this study, we assessed the effect of these systemic inflammatory markers on overall survival (OS) and disease-free survival (DFS) in patients with non-small cell lung cancer (NSCLC) who underwent radical resection with follow-up of at least 5 years.

**Methods**

**Study population**

We retrospectively reviewed a cohort of 653 patients who were treated with radical lung resection between January 2004 and December 2012. Patients with a history of systemic inflammatory disease, concomitant active infection, neoadjuvant treatment, preoperative stage $\geq T3$, preoperative stage $\geq N1$, patients lost to follow-up, or those for whom preoperative blood tests were not available were excluded (Fig. 1). Finally, we included 268 patients diagnosed with early clinical stage non-small cell lung cancer who underwent anatomic pulmonary resection with systematic lymph node dissection.

All patients underwent the same preoperative workup which included physical examination, full blood count and renal function tests, bronchoscopy, pulmonary function tests with diffusion studies, computed tomography (CT) and positron-emission tomography/computed tomography (PET-CT). All patients signed an informed consent form and the study was approved by the Institutional Review Board.

**Study variables**

The variables studied were age, sex, comorbidities (smoking, diabetes mellitus, ischaemic heart disease, chronic obstructive pulmonary disease, and hypertension), type of surgery performed, pathological stage, tumour histology, disease-free survival and overall survival. The study aims did not include the association between these markers and postoperative complications.

The lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were calculated from the absolute neutrophil, platelet, monocyte and lymphocyte counts from routine preoperative testing performed 1–2 weeks before surgery at the same hospital.

*Fig. 1* Flow chart of patient selection
Follow-up
Routine follow-up was carried out at 1 month after surgery and included a full panel of blood tests and chest X-ray, then every 6 months with CT chest for the first 3 years, with annual checks thereafter, as per hospital protocol. If recurrence was suspected after surgery, the relevant tests, eg PET-CT, MRI brain, were requested according to the clinical scenario. Recurrences were classified as locoregional or distant metastases based on imaging. Locoregional recurrence was defined as recurrence in mediastinal or hilar lymph nodes or ipsilateral lung. Other recurrences were defined as distant metastases. All patients were seen by specialists and discussed by the multidisciplinary team to decide on treatment planning. Diagnosis of recurrence or distant metastases was evaluated and confirmed in the multidisciplinary unit.

Statistical analysis
A descriptive analysis of the sample was performed as frequency and percentage for qualitative variables, and mean and standard deviation for quantitative variables if they followed a normal distribution (Kolmogorov–Smirnov, \( p \) value > 0.05), or median and interquartile range if not. Subsequently, Kaplan–Meier survival analysis was performed, and variables that were clinically relevant and statistically significant (Log rank \( p \) value < 0.05) and that did not show interaction between them were included in Cox regression. A receiver operating characteristics (ROC) analysis was performed to calculate the NLR, PLR, and LMR values that would have the greatest sensitivity and specificity. The statistical software SPSS v 16.0 was used.

Results
Two hundred and sixty-eight patients were included in the study, of whom 218 (81.3%) were men. The mean age was 62.9 ± 8.7 years. Clinical, surgical, and pathological features and blood values of the study population are shown in Table 1. Twenty-five patients (9.2%) received tumour-specific adjuvant treatment. The median follow-up time was 52 months. One hundred patients (37.3%) received recurrence, of whom 74 (27.6%) had distant metastases and 26 (9.7%) had locoregional recurrence. Twelve patients (4.5%) developed second primary lung tumours and underwent new radical surgery. One hundred and fifty-nine (57.3%) patients were still alive at the end of follow-up; 109 (42.7%) patients died.

Following ROC analysis, the values with the greatest sensitivity and specificity were 2.5 for NLR and LMR and 150 for PLR. Disease-free survival and OS were evaluated after splitting patients according to these proposed maker levels (Table 2). An LMR ≥ 2.5 was a clear prognostic factor for higher overall survival and lower

| Table 1 | Clinical, surgical, pathological and inflammatory parameters for the study population |
| --- | --- |
| Males | 268 (81.3%) |
| Age (years) | 62.9 ± 8.7 |
| Smoker | 205 (76.5%) |
| Diabetes mellitus | 57 (21.3%) |
| Ischaemic cardiomyopathy | 33 (12.3%) |
| COPD | 100 (37.3%) |
| Hypertension | 103 (38.4%) |
| Dyslipidaemia | 99 (36.9%) |
| Surgical procedure | |
| Lobectomy | 224 (83.6%) |
| Pneumonectomy | 14 (5.2%) |
| Sub‑lobar resection | 38 (11.2%) |
| Pathologic stage | |
| Ia/Ib | 173 (64.5%) |
| IIa/IIb | 74 (27.6%) |
| IIIa/IIIb | 19 (7.1%) |
| IV | 2 (0.8%) |
| Histological type | |
| Adenocarcinoma | 168 (62.7%) |
| Squamous cell carcinoma | 79 (29.5%) |
| Large cell carcinoma | 18 (6.7%) |
| Other | 3 (1.1%) |
| Neutrophils, × 10⁹/L | 4.47 (1.63) |
| Lymphocytes, × 10⁹/L | 2.14 (1.59) |
| Monocytes, × 10⁹/L | 0.57 (0.20) |
| Platelets, × 10⁹/L | 243 (79.71) |
| LMR | 3.97 (1.97) |
| NLR | 2.38 (1.23) |
| PLR | 131.59 (65.03) |

| Table 2 | Distribution of patients according to LMR |
| --- | --- |
| Study population, n: 268 | LMR < 2.5 | LMR ≥ 2.5 |
| No. of patients | 47 | 221 |
| No. of patients who died during the follow-up period | 28 | 81 |
| No. of patients who died or had recurrence during the follow-up period | 35 | 107 |

NLR, neutrophil-to-lymphocyte ratio, PLR, platelet-to-lymphocyte ratio, COPD, chronic obstructive pulmonary disease, LMR, lymphocyte-to-monocyte ratio

recurrence in patients with surgically-resected lung cancer (\( p = 0.001 \)) (Figs. 2, 3). On univariate analysis, age, pathological stage and LMR ≥ 2.5 were significantly associated with higher disease-free survival (HR, 0.444; 95%
CI 0.289–0.683; \( p = 0.001 \). These variables remained statistically significant on multivariate analysis (HR, 0.476; 95% CI 0.307–0.738; \( p = 0.001 \); Table 3) after adjusting for age, sex, pathological stage and histology.

Regarding overall survival, univariate analysis showed that age, pathological stage and LMR \( \geq 2.5 \) were associated with better overall survival (HR, 0.488; 95% CI 0.317–0.751; \( p = 0.001 \)). These variables were also significant on multivariate analysis (HR, 0.546; 95% CI 0.352–0.846; \( p = 0.007 \); Table 4) after adjusting for age, sex, pathological stage and histology. NLR and PLR were not found to be prognostic factors for overall survival or disease-free survival.

![Kaplan–Meier analysis of overall survival (OS) based on LMR](image)
Discussion
The association between inflammation and cancer was first described years ago and has been the subject of much study. O’Callaghan et al. [13] described the role of inflammation in the etiopathogenesis of lung cancer, and multiple studies have confirmed the prognostic value of inflammation in lung cancer outcomes, for both local and advanced disease [10, 14].

Our study included 268 patients who underwent resection and prospective follow-up for at least 5 years, and demonstrates that an LMR ≥ 2.5 is an independent positive prognostic factor for disease-free survival and overall survival. Although this ratio has not been studied extensively in cancer and particularly bronchogenic cancer, our findings are in line with those obtained by other groups. Xia et al. [15], in 439 patients with stage I...
NSCLC, demonstrated a positive association between LMR and overall survival and a greater risk of distal metastases with lower LMR. However, Asian populations may behave differently from European populations in terms of blood markers, so their results will need to be validated in a Western population.

In 2018, Chen et al. [16] published a series of 577 surgical patients in stage IB NSCLC who had undergone pneumonectomy. They found that LMR and PLR were independent prognostic factors for OS. In our series, LMR was an independent prognostic factor for OS and DFS. However, we did not find a statistically significant association for PLR as a prognostic factor. One explanation could be that the patients requiring pneumonectomy are usually patients with larger tumours or with greater intrapulmonary lymph node involvement, so they are likely to have higher baseline levels of inflammation. In our study only 5.2% of the patients had undergone pneumonectomy, while 100% of those in the study by Chen et al. had undergone pneumonectomy, with pleural invasion in 39% of the cases.

The immunological basis for our findings is that lymphoid cells play a primordial role in the control, proliferation, and migration of tumour cells [17]. In cervical cancer, it has been observed that lymphocytes act as

### Table 3 Univariate and multivariate analysis of disease-free survival (DFS)

| Covariables | Hazard ratio | 95% CI | p value |
|-------------|--------------|--------|---------|
| **Univariate analysis** | | | |
| PLR ≥ 150 | 0.986 | 0.654–1.488 | 0.948 |
| NLR ≥ 2.5 | 1.203 | 0.821–1.761 | 0.343 |
| LMR ≥ 2.5 | 0.444 | 0.289–0.683 | 0.001 |
| Age | 1.018 | 0.996–1.040 | 0.112 |
| Sex (female) | 0.970 | 0.595–1.579 | 0.901 |
| Pathological stage | | | 0.051* |
| Stage I | 1.000 | | |
| II | 1.686 | 1.126–2.526 | 0.011 |
| III | 1.793 | 0.812–3.958 | 0.148 |
| IV | 2.536 | 0.350–18.380 | 0.357 |
| Histological type | | | 0.219* |
| Adenocarcinoma | 1.000 | | |
| Squamous cell carcinoma | 0.618 | 0.384–0.995 | 0.048 |
| Large cell carcinoma | 0.792 | 0.381–1.646 | 0.532 |
| Other | 0.568 | 0.138–2.343 | 0.434 |
| **Multivariate analysis** | | | |
| LMR ≥ 2.5 | 0.476 | 0.307–0.738 | 0.001 |
| Age | 1.029 | 1.005–1.054 | 0.017 |
| Sex | | | |
| Male | 1.000 | | |
| Female | 1.171 | 0.693–1.977 | 0.556 |
| Pathological stage | | | 0.027* |
| Stage I | 1.000 | | |
| II | 1.779 | 1.174–2.695 | 0.007 |
| III | 1.878 | 0.848–4.162 | 0.120 |
| IV | 3.101 | 0.406–23.695 | 0.275 |
| Histological type | | | 0.053* |
| Adenocarcinoma | 1.000 | | |
| Squamous cell carcinoma | 0.527 | 0.322–0.862 | 0.011 |
| Large cell carcinoma | 0.619 | 0.294–1.301 | 0.205 |
| Other | 0.541 | 0.127–2.306 | 0.407 |

LMR lymphocyte-to-monocyte ratio, NLR neutrophil-to-lymphocyte ratio, PLR platelet-to-lymphocyte ratio

* Linear trend p value

### Table 4 Univariate and multivariate analysis of overall survival

| Covariables | Hazard ratio | 95% CI | p value |
|-------------|--------------|--------|---------|
| **Univariate analysis** | | | |
| PLR ≥ 150 | 1.151 | 0.772–1.715 | 0.494 |
| NLR ≥ 2.5 | 1.175 | 0.806–1.714 | 0.401 |
| LMR ≥ 2.5 | 0.488 | 0.317–0.751 | 0.001 |
| Age | 1.037 | 1.013–1.060 | 0.002 |
| Sex (female) | 0.831 | 0.481–1.436 | 0.507 |
| Pathological stage | | | 0.026* |
| Stage I | 1.000 | | |
| Stage II | 1.718 | 1.148–2.571 | 0.009 |
| Stage III | 1.980 | 0.975–4.017 | 0.059 |
| Stage IV | 2.296 | 0.317–16.631 | 0.411 |
| Histological type | | | 0.999* |
| Adenocarcinoma | 1.000 | | |
| Squamous cell carcinoma | 0.991 | 0.651–1.509 | 0.967 |
| Large cell carcinoma | 1.041 | 0.518–2.091 | 0.909 |
| Other | 0.986 | 0.135–7.190 | 0.989 |
| **Multivariate analysis** | | | |
| LMR ≥ 2.5 | 0.546 | 0.352–0.846 | 0.007 |
| Age | 1.041 | 1.017–1.066 | 0.001 |
| Sex | | | |
| Male | 1.000 | | |
| Female | 1.013 | 0.564–1.819 | 0.966 |
| Pathological stage | | | 0.013* |
| Stage I | 1.000 | | |
| II | 1.783 | 1.179–2.697 | 0.006 |
| III | 2.144 | 1.047–4.389 | 0.037 |
| IV | 4.083 | 0.521–31.995 | 0.180 |
| Histological type | | | 0.830* |
| Adenocarcinoma | 1.000 | | |
| Squamous cell carcinoma | 0.812 | 0.525–1.255 | 0.348 |
| Large cell carcinoma | 0.923 | 0.457–1.864 | 0.824 |
| Other | 0.929 | 0.122–7.056 | 0.943 |

LMR lymphocyte-to-monocyte ratio, NLR neutrophil-to-lymphocyte ratio, PLR platelet-to-lymphocyte ratio

* Linear trend p value
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Conclusions
The findings from this study in a cohort of patients who underwent surgery for NSCLC confirm that the lymphocyte-to-monocyte ratio is a convenient preoperative biomarker that could provide valuable information on the probability of recurrence and overall survival in this population.

Abbreviations
LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; OS: Overall survival; DFS: Disease-free survival; HR: Hazard ratio; NSCLC: Non-small cell lung cancer; CT: Computed tomography; PET-CT: Positron-emission tomography/computed tomography; ROC: Receiver operating characteristics.

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Authors’ contributions
RR and EN made substantial contributions to the design of this study. RR, IM, CD, FR, AU, CMa, and IE collected and analysed the data; RR, IM, ANM, CD, FR, AU, CMo and IE wrote the manuscript; RR revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
All patients signed an informed consent form. The study was approved by the Clinical Research Ethics Committee of Bellvitge University Hospital (CEIC). All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no conflict of interest.

Author details
1 Department of Thoracic Surgery; Hospital Universitari de Bellvitge, Bellvitge Biomedical Research Institute (IDIBELL), Feixa Llarga s/n., 08907 L’Hospitalet de Llobregat, Barcelona, Spain. 2 Department of Radiation Oncology, Catalan Institute of Oncology (ICO), Bellvitge Biomedical Research Institute (IDIBELL), L’Hospitalet de Llobregat, Barcelona, Spain. 3 Department of Preventive Medicine. Hospital Universitari de Bellvitge, Bellvitge Biomedical Research Institute (IDIBELL), L’Hospital de Llobregat, Barcelona, Spain. 4 Department of Medical Oncology, Catalan Institute of Oncology (ICO), L’Hospital de Llobregat, Barcelona, Spain. 5 Department of Thoracic Surgery; Hospital Universitari de Bellvitge, Bellvitge Biomedical Research Institute (IDIBELL), L’Hospital de Llobregat, Barcelona, Spain. 6 Unit of Human Anatomy, Department of Pathology and Experimental Therapeutics, Medical School, University of Barcelona, Barcelona, Spain.
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