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Prognostic Significance of Pretreatment Total Lymphocyte Count and Neutrophil-to-Lymphocyte Ratio in Extensive-Stage Small-Cell Lung Cancer

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Abstract

Background—We evaluated pretreatment total lymphocyte count (TLC, marker of immunosuppression), neutrophil-to-lymphocyte ratio (NLR, marker of inflammation), and overall survival (OS) in patients with extensive-stage small-cell lung cancer (ES-SCLC).

Methods—Pretreatment blood characteristics, age, sex, performance status, race, stage (M1a vs. M1b), number and location of metastases, weight loss, smoking status, chemotherapy cycles (<4 vs. 4), thoracic radiotherapy dose (<45 vs. 45 Gy), and receipt of prophylactic cranial irradiation (PCI) were evaluated in 252 patients with ES-SCLC treated in 1998–2015. Factors significant in univariate analysis were selected as covariates for a multivariate Cox model.

Results—Pretreatment TLC was below normal ($<1.0 \times 10^3/\mu\text{L}$) in 58 patients (23%). Median OS time was 11.0 months and was worse for those with TLC $1.5 \times 10^3/\mu\text{L}$ (9.8 vs. 12.0 months) and pretreatment NLR >4.0 (9.4 vs. 13.9 months). Multivariate analysis identified low TLC (hazard ratio [HR] 0.734, 95% confidence interval [CI] 0.565–0.955, $P=0.021$) and high NLR (HR 1.521, 95% CI 1.172–1.976, $P=0.002$) as predicting inferior survival. Age (>63 y), sex (male), performance status (≥ 2), chemotherapy cycles (<4), radiation dose (<45 Gy), and no PCI also predicted worse OS ($P<0.05$).

Conclusions—Pretreatment TLC and NLR may be useful for stratifying patients with ES-SCLC for treatment approaches.

Keywords

Prognostic factors; overall survival; hematologic marker; immune status; inflammation

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Introduction

Lung cancer is the second most common type of cancer and the leading cause of death among both women and men in the United States [1]. Although the incidence of small cell lung cancer (SCLC) has declined over the past decades, it still comprises 15% of all lung cancer cases, and 60% of patients present with extensive-stage (ES) disease [2]. SCLC is highly proliferative and prone to widespread metastases. Because of its aggressive nature and its common dissemination at diagnosis, treatment for ES-SCLC tends to be given with palliative intent, as the 5-year survival rate is only 2% and the median survival time only 6.1 months [2].

Chemotherapy was regarded as the mainstay of treatment until the 1980s, when the effectiveness of adding radiotherapy to systemic therapy was revealed [3]. The therapeutic plateau for chemotherapy seems to have been achieved with the introduction of platinum-etoposide doublet therapy [4]. Most of the advances in terms of disease control and survival benefit for SCLC at any stage during the past two decades have resulted from improvements in radiotherapy, particularly the addition of thoracic radiotherapy (TRT) and prophylactic cranial irradiation (PCI) [5–7]. More recently, the emergence of immunotherapy has brought a paradigm shift for lung cancer treatment [8].

Identifying reliable markers with which to better select patients for both currently available approaches and upcoming approaches such as immunotherapy would greatly aid clinical decision-making. Performance status (PS), age, and sex are well-established predictors in ES-SCLC [9]. However, no other relevant prognostic factors are available at present, especially as we anticipate use of immunologic therapies.

Immune and inflammatory responses in the body are critical for tumor development [10]. In immunocompetent patients, immunosurveillance prevents or inhibits tumor growth; however, immune suppression expressed as lymphopenia has been linked with poor survival in many malignancies such as breast cancer, sarcoma, lymphoma, cervical cancer, glioblastoma, pancreatic cancer, and non-small cell lung cancer (NSCLC) [11–17]. Treatment-related lymphopenia was found to be correlated with poor survival in one study of patients with limited-stage SCLC [18]. However, the effect of reduced lymphocyte counts at baseline on outcome for patients with ES-SCLC is still unknown.

In addition to immune suppression, inflammation can affect every aspect of tumor development and progression as well as the response to therapy [10]. Systemic inflammation has been linked with outcome in several types of cancer. Platelets have numerous roles in physiological and pathological pathways, including homeostasis and inflammation [19]. Several groups have reported that increased platelet counts correlated with dismal prognosis in patients with various types of cancer, including lung [19–23]. Other markers of inflammation and immunologic function including the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been linked with prognosis in a variety of malignancies such as cholangiocarcinoma, esophageal, colorectal, ovarian, and head and neck cancers [24–28]. The pertinence of NLR and PLR has also been demonstrated in both

NSCLC and SCLC [29, 30]; higher NLR generally implies worse outcome, but the implications of PLR have not been consistent in patients with SCLC.

The aim of this study was to investigate the influence of pretreatment immunologic and inflammatory hematologic markers (total lymphocyte count [TLC], platelet count, NLR, and PLR) as a manifestation of immune and systemic inflammation status on overall outcome in patients with ES-SCLC.

Methods

Patients

After review and approval of this study by the appropriate institutional review board, subjects were retrospectively identified from a database of SCLC patients treated at a single tertiary cancer center. Inclusion criteria were as follows: (1) pathologically confirmed SCLC, (2) pathologically or radiologically confirmed ES (i.e., TNM stage IV disease), (3) new diagnosis of ES-SCLC from May 1998 through September 2015, and (4) available data on baseline (pretreatment) complete blood count (CBC) with differentials obtained at our institution. In addition to tissue biopsy and laboratory tests, the initial diagnostic work-up included computed tomography (CT) of the chest and upper abdomen, brain magnetic resonance imaging (MRI) (or brain CT if MRI was contraindicated), bone scan, and positron emission tomography/CT. Patients with abnormal CBC findings underwent bone marrow aspiration. The standard practice at our institution is to administer 4–6 cycles of platinum chemotherapy. Patients who experienced response to this chemotherapy in the chest and at metastatic sites were offered consolidative TRT and PCI. Re-imaging of the brain (with MRI or CT if MRI was contraindicated) was required for patients who were candidates for PCI. Patients with brain metastases could receive whole-brain radiotherapy (WBRT) before or after chemotherapy depending on their symptoms. Patients who were not candidates for chemotherapy or had disease that progressed after chemotherapy were offered palliative TRT.

Data collection

Variables including clinicopathologic and treatment characteristics were extracted from the electronic medical records of patients in our SCLC database. Baseline CBC and blood chemistry findings were collected between the date of diagnosis and the initiation of any treatment (chemotherapy or radiotherapy [TRT or WBRT]). NLR was calculated by dividing the total neutrophil count by the TLC. Similarly, PLR was calculated dividing the total platelet count by the TLC. Patients were stratified according to the median values of the baseline hematologic markers (albumin [Alb], lactate dehydrogenase [LDH], white blood cell count [WBC], hemoglobin [Hb], platelets, neutrophils, TLC, NLR, and PLR). Other clinical characteristics were the date of diagnosis (1998–2005, 2006–2010, or 2011–2015), age (<63 or ≥63 years), sex, Eastern Cooperative Oncology Group [ECOG] PS score (0–1 vs. ≥2), race (white vs. non-white), TNM M status (M1a vs. M1b), number of metastases (1 vs. ≥2), presence of metastases in liver, brain, or bone, weight loss of ≥10%, tobacco smoking history (ever vs. never), current smoking status, number of initial chemotherapy cycles (0 vs. 1–3 vs. ≥4), dose of TRT (<45 Gy vs. ≥45 Gy), and receipt of PCI.

Statistical analysis

Clinicopathologic and treatment characteristics were summarized by using descriptive statistics. Differences between higher- and lower-TLC groups were compared with Chi-square tests or Mann–Whitney U tests as appropriate. The primary outcome of interest was overall survival (OS), which was calculated from the date of diagnosis to the date of death or last follow-up. The log-rank test was used to compare Kaplan–Meier estimates of survival between groups. All baseline clinical and treatment valuables except for ever-smoking status were evaluated as covariates. A univariate proportional hazard Cox model was used to assess potential associations between these characteristics and OS. To assess whether hematologic markers (including TLC and NLR) were independent predictors of survival, a multivariate Cox model was constructed using all of the other factors having a *P* value of 0.25 on univariate analysis, and each factor was eliminated using backwards elimination in a stepwise manner until the most significant variables were identified. The Wald test was used to assess the role of covariates in the model. Because of the strong co-linearity between TLC and NLR (Spearman's correlation coefficient 0.738), these factors could not be included simultaneously and were tested in separate models. All analyses were two-sided and significance was set at a *P* value of 0.05. Statistical analyses were done with SPSS Statistics 24 (SPSS Inc., Chicago, IL) and Stata/MP 14.2 statistical software (Stata Corp LP, College Station, TX).

Results

A total of 252 patients met the inclusion criteria and were included in the analysis (Table 1). The median patient age was 63 years [interquartile range (IQR) 56–69]; 53% of the patients were female and 27% had an ECOG score of 2. Seventy-five percent of the patients received 4 cycles of platinum-based chemotherapy; 45% received TRT to 45 Gy for consolidation or palliation; and 19% received PCI. No significant differences in these characteristics were found between patients who had TLC lower or higher than the median value with the following exceptions. More male patients (54%) had low (below-median-value) pretreatment TLC than did female patients (46%) (*P*=0.026); pretreatment Alb, WBC, Hb, and platelet count were generally lower in patients who had low TLC, and pretreatment LDH and neutrophil levels were generally higher in patients who had low TLC. These values were well within the normal range except for LDH, which slightly exceeded than the upper limit of normal [618 U/L] for patients with low TLC (Table 1). Regarding treatment details, 159 patients received TRT (63%), 113 (45%) receiving 45 Gy and 46 (18%) receiving <45 Gy; TRT was used for palliation or salvage in 78 patients (5 who were not candidates for chemotherapy, 10 who could not tolerate the full course of chemotherapy, 15 for symptom control before chemotherapy, 37 who experienced disease progression during chemotherapy and 11 with tumor recurrence within the chest after chemotherapy); and 95 patients received no TRT. As for chemotherapy, 12 patients received no chemotherapy, and 240 patients received some platinum-based chemotherapy (190 patients got 4 cycles and 50 patients got 1–3 cycles) (Table 1).

The median OS time for all patients was 11.0 months (95% confidence interval [CI] 10.1–12.0). Pretreatment TLC was below the lower limit of normal (i.e., $\text{TLC} < 1.0 \times 10^3/\mu\text{L}$) in 58

patients (23%). The median OS time was 9.8 months (95% CI 8.9–10.7) for patients with pretreatment TLC $1.5 \times 10^3/\mu\text{L}$ versus 12.0 months (95% CI 9.5–14.5) for patients with pretreatment TLC $>1.5 \times 10^3/\mu\text{L}$ (log-rank $P=0.013$, Fig 1a). On the other hand, the median OS time for patients with high pretreatment NLR (>4.0) was 9.4 months (95% CI 8.8–9.9) versus 13.9 months (95% CI 11.2–16.6) for patients with pretreatment NLR ≤ 4.0 (log-rank $P<0.001$, Fig 1b).

Fifteen factors were found to be associated with survival on univariate analysis: age, sex, ECOG score, number of metastases, having metastases in liver or bone, number of chemotherapy cycles, TRT dose, receipt of PCI, pretreatment Alb, LDH, platelet count, TLC, and NLR ($P<0.05$). No significant differences were observed in survival according to the date of diagnosis (1998–2005, 2006–2010, or 2011–2015). Having a high pretreatment PLR was not associated with survival (hazard ratio [HR] 1.196, 95% CI 0.926–1.545, $P=0.169$) (Table 2).

The final multivariate analysis indicated that low pretreatment TLC (HR 0.734, 95% CI 0.565–0.955, $P=0.021$) and high pretreatment NLR (HR 1.521, 95% CI 1.172–1.976, $P=0.002$) were independent predictors of inferior survival. Six other clinicopathologic characteristics (age >63 , being male, having an ECOG score ≥ 2 , <4 initial chemotherapy cycles, <45 Gy TRT, and no PCI) were also shown to be independent predictors of worse OS in multivariate analysis ($P<0.05$) (Table 3).

Pretreatment platelet counts were below the lower limit of normal (i.e., $<140 \times 10^9/\text{L}$) in 13 patients (5%). Although platelet count was significant in univariate analysis, with counts $>291 \times 10^9/\text{L}$ linked with better prognosis (HR 0.693, 95% CI 0.534–0.900, $P=0.006$), this apparent association did not hold in multivariate analysis (Tables 2 and 3).

Discussion

We found that both pretreatment TLC and NLR were useful predictors of outcome in patients treated for ES-SCLC. The relevance of pretreatment NLR noted in previous studies was confirmed. To our knowledge, this is the first study to show the importance of pretreatment TLC for predicting outcomes in patients with ES-SCLC. Neither pretreatment platelet counts nor PLR were linked with OS in this study.

NLR and PLR are markers of inflammation and immune status and have been recognized as prognostic indicators in various malignancies including lung cancer [24–29]. Findings are relatively consistent that higher NLR implies worse outcome, although the implications of PLR are not consistent in SCLC. Two single-institution studies investigated pretreatment NLR and PLR in patients with SCLC (both limited-stage [LS] and ES) [31,32]. Most of the patients in those studies (62%–64%) had ES-SCLC, and both studies found pretreatment NLR, but not PLR, to be an independent predictor of prognosis. Similar results were observed in another study in which 65% of patients had ES-SCLC [33]. Another single-institution study that examined patients with ES-SCLC and LS-SCLC separately [30] showed that pretreatment NLR was significant only for patients with ES-SCLC, but pretreatment PLR was significant only for patients with LS-SCLC.

From these results, one can assume some consistency in the prognostic value of pretreatment NLR in SCLC, but the value of pretreatment PLR, if any, remains undetermined. Nevertheless, pretreatment PLR could be an important factor for patients with LS-SCLC [30]. Three other single-institution studies of patients with predominantly LS-SCLC [34–36] included one study of only LS-SCLC patients, and more than half of the patients in the other two studies (56%–60%) had LS-SCLC (one of the latter two studies included patients with combined SCLC histology). Results of those studies showed that pretreatment NLR, but not PLR, was an independent predictor of prognosis. However, all of these studies had relatively small numbers of LS-SCLC patients ($n=62-82$), and these numbers may have been too small to detect possible associations of PLR and outcome. Our findings that pretreatment NLR, but not PLR, were predictive of outcome in patients with ES-SCLC are consistent with those of previous studies. Although more studies are needed to confirm the importance of pretreatment NLR and PLR in SCLC outcomes, we could speculate that pretreatment NLR may be useful for predicting outcome in ES-SCLC. Although pretreatment PLR does not seem to be a useful predictor in ES-SCLC, it could well be of use in patients with LS-SCLC.

Although not significant in multivariate analysis, our results did suggest that high pretreatment platelet counts ($>291 \times 10^9/L$) may have a protective effect with regard to OS. This finding seems counterintuitive, because the link between high platelet counts, enhanced inflammation, and tumor progression would suggest the opposite result. We did analyze whether use of chemotherapy (0 vs. any and 1–3 cycles vs. 4 cycles) was related to pretreatment platelet counts being under or over the lower limit of normal ($140 \times 10^9/L$), or under or over the median value ($291 \times 10^9/L$), and we found no statistically significant difference in terms of chemotherapy use in any of these subgroup analyses (Chi-square test, P value >0.05 , data not shown). Many studies have reported links between high platelet counts and dismal prognosis in patients with various types of cancer, including lung [19–23], with only a few showing it to be a favorable prognostic factor [37].

We speculate that the discrepancy in the implication of pretreatment platelet count between our study and other previous studies is the following. In cancers that are prone to wide systemic dissemination like ES-SCLC, the circumstances that drive the production of platelets, a marker of inflammation, to be higher or lower may be different than the circumstances in other less aggressive types of cancer. In ES-SCLC, large numbers of platelets might be “wasted” in coagulation within the microvessels, which would lead to the multiple organ failure characteristic of end-stage disease. The prognostic implications of platelet count may be different in LS- versus ES-SCLC. This postulated difference in the behavior of platelets may explain the heterogeneity in results regarding the association—or lack thereof—between PLR and outcomes in SCLC.

In our study, we found that 58 patients (23%) had pretreatment TLC less than the lower limit of normal ($1.0 \times 10^3/\mu L$), and we found that pretreatment TLC less than the median of $1.5 \times 10^3/\mu L$ predicted worse outcome. The high frequency of baseline lymphopenia and its adverse outcome in cancer patients have been reported in several previous studies [11,12,38]. In one such study of baseline TLC in advanced breast cancer, sarcoma, and lymphoma, the incidence of baseline lymphopenia ($<1.0 \times 10^3/\mu L$) was 24%–27% and lymphopenia was an independent predictor of both OS and progression-free survival [12].

Another group studied pretreatment TLC in patients with locally advanced cervical cancer and found a 15% incidence of pretreatment lymphopenia being $<1.0 \times 10^3/\mu\text{L}$, and survival among those patients was poor [11]. Another analysis of patients with NSCLC, colorectal cancer, or breast cancer showed that 43% had TLC $<1.5 \times 10^3/\mu\text{L}$ at baseline and that this low baseline TLC correlated with lesser effectiveness of chemotherapy [38]. Associations between treatment-related lymphopenia and OS have also been reported for several types of cancer, including LS-SCLC [13–18].

These findings and our own regarding the negative effect of low pretreatment TLC on outcome bolster the justification for ongoing research to develop vaccines and other immunologic therapies to treat cancer. The treatment of lung cancer, among others, has seen a paradigm shift with the advent of immunotherapy [8], and use of immune checkpoint blockade has shown promise in NSCLC. The phase I/II trial CheckMate 032, in which immune checkpoint inhibitors were used to treat relapsed SCLC, provided strong evidence of the potential of these drugs for SCLC treatment [39]. The results of the ongoing phase III trial CheckMate 331 (NCT02481830) are eagerly awaited. Future clinical trials investigating immunotherapy for lung cancer, including SCLC, could incorporate the use of hematologic markers such as pretreatment TLC and NLR as stratification factors.

This study was limited by its retrospective nature, the relatively small numbers of eligible patients, and the heterogeneity of those patients. Accordingly, larger prospective studies are needed to confirm our results.

In summary, our findings suggest that pretreatment TLC and NLR are important prognostic factors for patients with ES-SCLC. These findings strengthen the existing evidence that baseline immune suppression and systemic inflammation are associated with inferior clinical outcomes. Better understanding of the mechanisms underlying immune suppression and systemic inflammation may lead to the identification of novel therapeutic strategies, such as approaches that preserve normal immune function and prevent systemic inflammation, to improve survival among patients with ES-SCLC.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017; 67(1):7–30. [PubMed: 28055103]
2. Gaspar LE, McNamara EJ, Gay EG, et al. Small-cell lung cancer: prognostic factors and changing treatment over 15 years. *Clin Lung Cancer*. 2012; 13(2):115–22. [PubMed: 22000695]
3. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med*. 1992; 327(23):1618–24. [PubMed: 1331787]
4. Pietanza MC, Byers LA, Minna JD, Rudin CM. Small cell lung cancer: will recent progress lead to improved outcomes? *Clin Cancer Res*. 2015; 21(10):2244–55. [PubMed: 25979931]
5. Slotman B, Faivre-Finn C, Kramer G, et al. ; EORTC Radiation Oncology Group and Lung Cancer Group. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med*. 2007; 357(7):664–72. [PubMed: 17699816]

6. Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet*. 2015; 385:36–42. [PubMed: 25230595]
7. Woolf DK, Slotman BJ, Faivre-Finn C. The current role of radiotherapy in the treatment of small cell lung cancer. *Clin Oncol (R Coll Radiol)*. 2016; 28(11):712–719. [PubMed: 27522475]
8. Marrone KA, Naidoo J, Brahmer JR. Immunotherapy for lung cancer: no longer an abstract concept. *Semin Respir Crit Care Med*. 2016; 37(5):771–782. [PubMed: 27732998]
9. Foster NR, Mandrekar SJ, Schild SE, et al. Prognostic factors differ by tumor stage for small cell lung cancer: a pooled analysis of North Central Cancer Treatment Group trials. *Cancer*. 2009; 115(12):2721–31. [PubMed: 19402175]
10. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell*. 2010; 140(6):883–99. [PubMed: 20303878]
11. Wu ES, Oduyebo T, Cobb LP, et al. Lymphopenia and its association with survival in patients with locally advanced cervical cancer. *Gynecol Oncol*. 2016; 140(1):76–82. [PubMed: 26571200]
12. Ray-Coquard I, Cropet C, Van Glabbeke M, et al. European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas. *Cancer Res*. 2009; 69(13):5383–91. [PubMed: 19549917]
13. Mendez JS, Govindan A, Leong J, Gao F, Huang J, Campian JL. Association between treatment-related lymphopenia and overall survival in elderly patients with newly diagnosed glioblastoma. *J Neurooncol*. 2016; 127(2):329–35. [PubMed: 26725885]
14. Grossman SA, Ellsworth S, Campian J, et al. Survival in patients with severe lymphopenia following treatment with radiation and chemotherapy for newly diagnosed solid tumors. *J Natl Compr Canc Netw*. 2015; 13(10):1225–31. [PubMed: 26483062]
15. Wild AT, Ye X, Ellsworth SG, et al. The association between chemoradiation-related lymphopenia and clinical outcomes in patients with locally advanced pancreatic adenocarcinoma. *Am J Clin Oncol*. 2015; 38(3):259–65. [PubMed: 23648440]
16. Tang C, Liao Z, Gomez D, et al. Lymphopenia association with gross tumor volume and lung V5 and its effects on non-small cell lung cancer patient outcomes. *Int J Radiat Oncol Biol Phys*. 2014; 89(5):1084–91. [PubMed: 25035212]
17. Campian JL, Ye X, Brock M, Grossman SA. Treatment-related lymphopenia in patients with stage III non-small-cell lung cancer. *Cancer Invest*. 2013; 31(3):183–8. [PubMed: 23432821]
18. Cho O, Oh YT, Chun M, Noh OK, Lee HW. Radiation-related lymphopenia as a new prognostic factor in limited-stage small cell lung cancer. *Tumour Biol*. 2016; 37(1):971–8. [PubMed: 26264618]
19. Buergy D, Wenz F, Groden C, Brockmann MA. Tumor-platelet interaction in solid tumors. *Int J Cancer*. 2012; 130(12):2747–60. [PubMed: 22261860]
20. Shimada H, Oohira G, Okazumi S, et al. Thrombocytosis associated with poor prognosis in patients with esophageal carcinoma. *J Am Coll Surg*. 2004; 198(5):737–41. [PubMed: 15110807]
21. Brockmann MA, Giese A, Mueller K, et al. Preoperative thrombocytosis predicts poor survival in patients with glioblastoma. *Neuro Oncol*. 2007; 9(3):335–42. [PubMed: 17504931]
22. Gorelick C, Andikyan V, Mack M, Lee YC, Abulafia O. Prognostic significance of preoperative thrombocytosis in patients with endometrial carcinoma in an inner-city population. *Int J Gynecol Cancer*. 2009; 19(8):1384–9. [PubMed: 20009894]
23. Pedersen LM, Milman N. Prognostic significance of thrombocytosis in patients with primary lung cancer. *Eur Respir J*. 1996; 9(9):1826–30. [PubMed: 8880098]
24. Kitano Y, Yamashita YI, Yamamura K, et al. Effects of preoperative neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios on survival in patients with extrahepatic cholangiocarcinoma. *Anticancer Res*. 2017; 37(6):3229–3237. [PubMed: 28551669]
25. Yodying H, Matsuda A, Miyashita M, et al. Prognostic significance of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in oncologic outcomes of esophageal cancer: a systematic review and meta-analysis. *Ann Surg Oncol*. 2016; 23(2):646–54. [PubMed: 26416715]

26. Pedrazzani C, Mantovani G, Fernandes E, et al. Assessment of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and platelet count as predictors of long-term outcome after R0 resection for colorectal cancer. *Sci Rep*. 2017; 7(1):1494. [PubMed: 28473700]
27. Prodromidou A, Andreakos P, Kazakos C, Vlachos DE, Perrea D, Pergialiotis V. The diagnostic efficacy of platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in ovarian cancer. *Inflamm Res*. 2017; 66(6):467–475. [PubMed: 28260123]
28. Turri-Zanoni M, Salzano G, Lambertoni A, et al. Prognostic value of pretreatment peripheral blood markers in paranasal sinus cancer: neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio. *Head Neck*. 2017; 39(4):730–736. [PubMed: 28032937]
29. Yang HB, Xing M, Ma LN, Feng LX, Yu Z. Prognostic significance of neutrophil-lymphocyteratio/platelet-lymphocyteratio in lung cancers: a meta-analysis. *Oncotarget*. 2016; 7(47):76769–76778. [PubMed: 27732958]
30. Xie D, Marks R, Zhang M, et al. Nomograms predict overall survival for patients with small-cell lung cancer incorporating pretreatment peripheral blood markers. *J Thorac Oncol*. 2015; 10(8):1213–20. [PubMed: 26200277]
31. Deng M, Ma X, Liang X, Zhu C, Wang M. Are pretreatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio useful in predicting the outcomes of patients with small-cell lung cancer? *Oncotarget*. 2017; 8(23):37200–37207. [PubMed: 28380461]
32. Kang MH, Go SI, Song HN, et al. The prognostic impact of the neutrophil-to-lymphocyte ratio in patients with small-cell lung cancer. *Br J Cancer*. 2014; 111(3):452–60. [PubMed: 24921916]
33. Shao N, Cai Q. High pretreatment neutrophil-lymphocyte ratio predicts recurrence and poor prognosis for combined small cell lung cancer. *Clin Transl Oncol*. 2015; 17(10):772–8. [PubMed: 26243392]
34. Käsmann L, Bolm L, Schild SE, Janssen S, Rades D. Neutrophil-to-lymphocyte ratio predicts outcome in limited disease small-cell lung cancer. *Lung*. 2017; 195(2):217–224. [PubMed: 28154994]
35. Wang X, Teng F, Kong L, Yu J. Pretreatment neutrophil-to-lymphocyte ratio as a survival predictor for small-cell lung cancer. *Onco Targets Ther*. 2016; 9:5761–5770. [PubMed: 27703374]
36. Wang X, Jiang R, Li K. Prognostic significance of pretreatment laboratory parameters in combined small-cell lung cancer. *Cell Biochem Biophys*. 2014; 69(3):633–40. [PubMed: 24554485]
37. Domínguez I, Crippa S, Thayer SP, et al. Preoperative platelet count and survival prognosis in resected pancreatic ductal adenocarcinoma. *World J Surg*. 2008; 32(6):1051–6. [PubMed: 18224462]
38. Lissoni P, Brivio F, Fumagalli L, et al. Efficacy of cancer chemotherapy in relation to the pretreatment number of lymphocytes in patients with metastatic solid tumors. *Int J Biol Markers*. 2004; 19(2):135–40. [PubMed: 15255546]
39. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol*. 2016; 17(7):883–95. [PubMed: 27269741]

Figure 1.

Kaplan-Meier plot of survival stratified by pretreatment total lymphocyte count (TLC) (a) or pretreatment neutrophil-to-lymphocyte ratio (NLR) (b). Overall survival was significantly worse for patients with lower pretreatment TLC and higher pretreatment NLR.

Table 1

Patient characteristics

Characteristic	All Patients	P Value	Patients with TLC 1.5×10 ³ /μL	Patients with TLC 1.5×10 ³ /μL	
No. of patients (%)	252	(100)	136	(54)	116 (46)
Age at diagnosis, years, median (IQR)	63	(56–69)	63	(56–68)	63 (55–70)
0.951					
Sex					
Male	119	(47)	73	(54)	46 (40) 0.026
Female	133	(53)	63	(46)	70 (60)
ECOG performance status					
0–1	185	(73)	95	(70)	90 (78) 0.166
2	67	(27)	41	(30)	26 (22)
Race					
White	214	(85)	117	(86)	97 (84) 0.594
Non-white	38	(15)	19	(14)	19 (16)
Weight loss ≥10%					
Yes	48	(19)	31	(23)	17 (15) 0.101
No	204	(81)	105	(77)	99 (85)
Ever smoker					
Yes	247	(98)	134	(99)	113 (97) 0.527
No	5	(2)	2	(1)	3 (3)
Current smoker					
Yes	86	(34)	46	(34)	40 (34) 0.963
No	158	(63)	85	(63)	73 (63)
Unknown	8	(3)	5	(4)	3 (3)
TNM M status					
M1a	18	(7)	8	(6)	10 (9) 0.400
M1b	234	(93)	128	(94)	106 (91)
No. of metastases					
1	40	(16)	17	(13)	23 (20) 0.113
>1	212	(84)	119	(88)	93 (80)
Metastasis to liver					
No	150	(60)	78	(57)	72 (62) 0.447
Yes	102	(40)	58	(43)	44 (38)
Metastasis to brain					
No	167	(66)	88	(65)	79 (68) 0.570
Yes	85	(34)	48	(35)	37 (32)
Metastasis to bone					
No	143	(57)	76	(56)	67 (58) 0.764
Yes	109	(43)	60	(44)	49 (42)
No. of cycles of first-line platinum-based chemotherapy					

Characteristic >1.5×10 ³ /μL	All Patients <i>P</i> Value	Patients with TLC 1.5×10 ³ /μL	Patients with TLC 1.5×10 ³ /μL	
0	12 (5)	7 (5)	5 (4)	0.104
1–3	50 (20)	32 (24)	18 (16)	
4	190 (75)	97 (71)	93 (80)	
Receipt of thoracic RT				
0 Gy	93 (37)	54 (40)	39 (34)	0.202
1–45 Gy	46 (18)	25 (18)	21 (18)	
45 Gy	113 (45)	57 (42)	56 (48)	
Prophylactic cranial irradiation				
Yes	49 (19)	24 (18)	25 (22)	0.435
No	203 (81)	112 (82)	91 (78)	
Pretreatment Alb, g/dL, median (IQR) ^a	4.0 (3.6–4.3)	3.9 (3.5–4.2)	4.0 (3.7–4.3)	
0.002				
Pretreatment LDH, IU/L, median (IQR) ^b	626 (514–894)	697 (515–1114)	595 (512–772)	
0.019				
Pretreatment WBC, ×10 ³ /μL, median (IQR)	8.6 (6.7–10.9)	8.5 (6.3–10.9)	9.1 (7.2–10.9)	
0.265				
Pretreatment Hb, g/dL, median (IQR)	13.2 (12.2–13.9)	12.8 (12.1–13.8)	13.5 (12.6–14.2)	
<0.001				
Pretreatment platelets, ×10 ⁹ /L, median (IQR)	291 (216–373)	262 (201–370)	307 (245–375)	
0.013				
Pretreatment neutrophils, ×10 ³ /μL, median (IQR)	6.2 (4.4–8.1)	6.5 (4.5–9.3)	5.9 (4.2–7.3)	
0.040				
Pretreatment TLC, ×10 ³ /μL, median (IQR)	1.5 (1.0–1.9)	1.1 (0.8–1.2)	2.0 (1.7–2.4)	
<0.001				
Pretreatment NLR, median (IQR)	4.0 (2.6–6.7)	6.4 (3.9–10.4)	2.8 (2.1–3.8)	
<0.001				
Pretreatment PLR, median (IQR)	194.7 (138.1–279.4)	254.8 (191.2–362.7)	140.6	
(114.1–190.1)	<0.001			

^aData for 8 patients were unavailable

^bData for 3 patients were unavailable.

Abbreviations: TLC, total lymphocyte count; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; RT, radiation therapy; Alb, albumin; LDH, lactate dehydrogenase; WBC, white blood cell; Hb, hemoglobin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio

Table 2

Univariate analysis of potential associations between patient characteristics and survival

Variable	Hazard Ratio	95% CI	P Value
Diagnosis Date			
1998–2005	1.00		
2006–2010	0.794	0.569–1.106	0.173
2011–2015	0.835	0.600–1.161	0.283
Age			
<63	1.00		
63	1.445	1.117–1.870	0.005
Sex			
Male	1.00		
Female	0.702	0.542–0.909	0.007
ECOG			
0–1	1.00		
2	1.642	1.232–2.190	0.001
Race			
White	1.00		
Non-white	0.857	0.596–1.234	0.408
M status			
M1a	1.00		
M1b	1.324	0.807–2.170	0.266
No. of metastases			
1	1.00		
>1	1.549	1.075–2.230	0.019
Metastasis to liver			
No	1.00		
Yes	1.439	1.108–1.868	0.006
Metastasis to brain			
No	1.00		
Yes	1.190	0.909–1.558	0.206
Metastasis to bone			
No	1.00		
Yes	1.526	0.173–1.983	0.002
Weight loss ≥10%			
No	1.00		
Yes	1.160	0.840–1.603	0.367
Current smoking			
No	1.00		
Yes	1.025	0.782–1.343	0.859
No. of chemotherapy cycles			
<4	1.00		

Variable	Hazard Ratio	95% CI	P Value
4	0.401	0.297–0.540	<0.001
Thoracic RT dose			
<45 Gy	1.00		
45 Gy	0.483	0.372–0.628	<0.001
Prophylactic cranial irradiation			
No	1.00		
Yes	0.474	0.337–0.666	<0.001
Pretreatment Alb			
4.0 g/dl	1.00		
>4.0 g/dl	0.711	0.546–0.926	0.011
Pretreatment LDH			
626 IU/L	1.00		
>626 IU/L	1.418	1.095–1.836	0.008
Pretreatment WBC			
$8.6 \times 10^3/\mu\text{L}$	1.00		
$>8.6 \times 10^3/\mu\text{L}$	1.161	0.900–1.497	0.252
Pretreatment Hb			
13.2 g/dL	1.00		
>13.2 g/dL	0.806	0.622–1.043	0.102
Pretreatment platelets			
$291 \times 10^9/\text{L}$	1.00		
$>291 \times 10^9/\text{L}$	0.693	0.534–0.900	0.006
Pretreatment neutrophils			
$6.2 \times 10^3/\mu\text{L}$	1.00		
$>6.2 \times 10^3/\mu\text{L}$	1.168	0.906–1.507	0.230
Pretreatment TLC			
$1.5 \times 10^3/\mu\text{L}$	1.00		
$>1.5 \times 10^3/\mu\text{L}$	0.723	0.559–0.935	0.013
Pretreatment NLR			
4.0	1.00		
>4.0	1.635	1.265–2.113	<0.001
Pretreatment PLR			
194.7	1.00		
>194.7	1.196	0.926–1.545	0.169

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; RT, radiation therapy; Alb, albumin; LDH, lactate dehydrogenase; WBC, white blood cell; Hb, hemoglobin; TLC, total lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table 3

Multivariate analysis of potential associations between patient characteristics and survival

Variable	Model 1 Hazard Ratio	95% CI	P value	Model 2 Hazard Ratio	95% CI	P value
Age						
63	1.00			1.00		
>63	1.457	1.118–1.899	0.005	1.455	1.116–1.898	0.006
Sex						
Male	1.00			1.00		
Female	0.757	0.581–0.987	0.040	0.762	0.585–0.993	0.044
ECOG						
0–1	1.00			1.00		
2	1.386	1.032–1.862	0.030	1.380	1.030–1.853	0.032
No. of initial platinum chemotherapy cycles						
<4	1.00			1.00		
4	0.509	0.373–0.696	<0.001	0.513	0.375–0.702	<0.001
Thoracic RT dose						
<45 Gy	1.00			1.00		
45 Gy	0.503	0.386–0.656	<0.001	0.524	0.402–0.684	<0.001
Prophylactic cranial irradiation						
No	1.00			1.00		
Yes	0.597	0.418–0.853	0.005	0.587	0.411–0.839	0.003
Pretreatment TLC						
1.5×10 ³ /μL	1.00			–		
>1.5×10 ³ /μL	0.734	0.565–0.955	0.021	–	–	–
Pretreatment NLR						
4.0	–			1.00		
>4.0	–	–	–	1.521	1.172–1.976	0.002

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; RT, radiation therapy; TLC, total lymphocyte count; NLR, neutrophil-to-lymphocyte ratio.