Prognostic significance of neutrophil-to-lymphocyte ratio in patients with malignant pleural mesothelioma: a meta-analysis

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ABSTRACT

Systemic inflammation responses can be reflected by peripheral blood count and combine index like the neutrophil-to-lymphocyte (NLR). The NLR has been reported to be a poor prognostic indicator in cancer recently. However, the prognostic effect of the NLR in patients with malignant pleural mesothelioma (MPM) still unclear yet. We conducted this meta-analysis aiming to evaluate the pooled value of NLR in prognosis as well as clinical characteristics in malignant pleural mesothelioma. A total of 11 studies with 1533 patients were included in this meta-analysis, in which 10 studies investigated the prognosis role of NLR using hazard ratio (HR) and 95% confidence intervals (95% CI). The elevated NLR was detected to be associated with a poor overall survival (OS) (HR=1.48, 95%CI=1.16-1.89, P < 0.001). The significant prognostic roles of NLR were also indicated in subgroup analyses. NLR level was also associated with histology instead of gender, stage or performance status (PS) score. These findings suggested that the elevated NLR could be a potential prognostic factor for malignant pleural mesothelioma patients and might be associated with histology as an efficient clinical index to stratify patients.

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a high aggressive tumor originates from mesothelial surfaces with a poor prognosis and a median survival of 9 to 13 months [1], and there were still no reliable prognostic indicators. Several prognostic biomarkers have been reported in the literature which including hemoglobin and white blood cell counts, performance status according to the Eastern Cooperative Oncology Group (ECOG) scale, age, weight loss, disease stage and imaging results (tumor volume, metabolic activity) to distinguish patients with good prognosis from those with inferior outcomes [2, 3]. Although these results for the prognosis helpful, but they were far from enough to predict the survival outcomes. Therefore, studies to further identify novel prognostic factors associated with accuracy and efficiency calls for the exertion of clinicians.

Inflammatatory responses have been found associated with tumor progression, evidence also shown that increased systemic inflammation was associated with poor overall survival (OS) in numerous types of cancer [4-9]. Inflammation is a crucial component of tumor microenvironment [8]. Inflammatory cells in the tumor microenvironment have important effects on tumor development, and markers of systemic inflammation may provide significant information for prognostication. Accumulating evidence suggested inflammation-related cells correlated closely with cancer are including neutrophils [10, 11], platelets [12], and lymphocytes [13]. Neutrophil to lymphocyte ratio (NLR), calculated as a simple ratio between neutrophil and lymphocyte counts, an index of systemic inflammation, has been related to poor survival for a variety of malignant tumors as renal cell carcinoma, colorectal cancer, hepatocellular carcinoma, prostate cancer and gastric cancer [14-18].
Therefore, it is a reasonable assumption that these two factors together might be applied as a prognostic factor. Here, we conducted a meta-analysis aiming to further verify the pooled prognostic value of NLR in malignant pleural mesothelioma.

RESULTS

Study characteristics and qualities

The flow chart of selection process was shown in Figure 1. We initially retrieved 380 studies in total without duplicates. After further screening, 365 studies were excluded for conference abstracts, case reports, reviews, or studies unrelated to this meta-analysis. Then, 15 studies were identified for the next step of evaluation with full text. During the further analysis, 4 studies [19, 20, 21, 22] were ruled out because they were failed to present specific NLR data for OS, not available in neither univariate nor multivariate analysis, or failed to estimate via sufficient information for HR and 95%CI, or studies with overlapping patients. Thus, finally 11 studies with 1533 patients were included in our meta-analysis, in which 10 studies [23-32] valuated the association between NLR and survival of malignant pleural mesothelioma patients, four study [23, 27, 29, 31] were included for investigation of NLR and patients’ clinical characteristics. The publication time ranged from 2010 to 2016. The ethnicities of the studies contained Asian and Caucasian. We extracted HR and 95%CI from multivariate analysis in seven studies and univariate analysis in three studies. All included studies reported data for OS. The study quality was evaluated via Newcastle-Ottawa scale, and the scores of the 11 studies ranged from 6 to 8. The main characteristics were shown in Table 1.

![Flow chart of study selection](image-url)

**Figure 1: The flow chart of study selection.** NLR: neutrophil-to-lymphocyte; OS: overall survival; HR: hazard ratio; CI: confidence intervals.
### Table 1: The baseline characteristics of included studies.

| Author     | Year | Country | Ethnicity | N  | Study design | Stage          | Treatment                                      | Cut-off value | Analysis | NOS score |
|------------|------|---------|-----------|----|--------------|----------------|------------------------------------------------|---------------|----------|-----------|
| Abakay     | 2014 | Turkey  | Caucasian | 155| Retrospective | NA/IV          | Chemotherapy/best supportive care               | 3             | NA       | 8         |
| Cedres     | 2014 | Spain   | Caucasian | 52 | Retrospective | III/IV         | Surgery/Chemotherapy/Radiotherapy                | 5             | MV       | 6         |
| Cihan      | 2014 | Turkey  | Caucasian | 50 | Retrospective | I/II/III/IV    | Surgery/Chemotherapy/Radiotherapy                | 3             | UV       | 6         |
| Hooper     | 2015 | the UK  | Caucasian | 73 | Prospective  | I/II/III/IV    | Chemotherapy/best supportive care               | 4             | MV       | 8         |
| Kao        | 2013 | Australia | Caucasian | 148| Retrospective | I/II/III/IV    | Surgery/Chemotherapy/Radiotherapy                | 3             | MV       | 6         |
| Kao        | 2011 | Australia | Caucasian | 85 | Retrospective | I/II/III/IV    | Surgery/neoadjuvant chemotherapy                | 3             | MV       | 7         |
| Kao        | 2010 | Australia | Caucasian | 173| Retrospective | I/II/III/IV    | First-line/second/third-line chemotherapy       | 5             | MV       | 8         |
| Meniawy    | 2013 | Australia | Caucasian | 274| Retrospective | I/II/III/IV    | Surgery/Chemotherapy/best supportive care       | 5             | MV       | 7         |
| Pinato     | 2012 | the UK   | Caucasian | 171| Retrospective | I/II/III/IV    | Chemotherapy/best supportive care               | 5             | MV       | 8         |
| Tanrikulu  | 2015 | Turkey   | Caucasian | 202| Retrospective | I/II/III/IV    | Chemotherapy/best supportive care               | 3             | MV       | 6         |
| Yamagishi  | 2015 | Japan    | Asian     | 150| Retrospective | I/II/III/IV    | Surgery/Chemotherapy/Radiotherapy/best supportive care | 5             | UV       | 6         |

*a* Number of included patients  
NA: not available; OS: overall survival; MV: multivariate analysis; UV: univariate analysis; NOS: Newcastle-Ottawa Quality Assessment Scale.

### Table 2: The pooled data on survival of meta-analysis

| Variables            | N<sup>b</sup> | Case<sup>b</sup> | Pooled data | Heterogeneity |
|----------------------|---------------|------------------|-------------|---------------|
|                      |               |                  | HR(95%CI)   | P             | F             | Ph             |
| Overall              | 10            | 1378             | 1.483(1.164-1.889) | 0.001         | 78.3%         | <0.001         |
| Ethnicity            |               |                  |             |               |               |                |
| Caucasian            | 9             | 1228             | 1.437(1.112-1.857) | 0.006         | 78.6%         | <0.001         |
| Asian                | 1             | 150              | 1.930(1.278-2.915) | 0.002         | NA            | NA             |
| Study design         |               |                  |             |               |               |                |
| Retrospective        | 9             | 1305             | 1.537(1.138-2.076) | 0.005         | 75.5%         | <0.001         |
| Prospective          | 1             | 73               | 1.170(1.065-1.286) | 0.001         | NA            | NA             |
| Survival analysis    |               |                  |             |               |               |                |
| Multivariate         | 8             | 1178             | 1.499(1.151-1.953) | 0.003         | 80.4%         | <0.001         |
| Univariate           | 2             | 200              | 1.261(0.473-3.362) | 0.644         | 75.4%         | 0.044          |
| Sample size          |               |                  |             |               |               |                |
| ≤149                 | 5             | 408              | 1.368(0.948-1.973) | 0.094         | 62.2%         | 0.032          |
| >149                 | 5             | 970              | 1.583(1.067-2.349) | 0.022         | 84.6%         | <0.001         |
| Cut-off value        |               |                  |             |               |               |                |
| 3                    | 4             | 485              | 1.358(0.844-2.185) | 0.207         | 71.9%         | 0.014          |
| 4                    | 1             | 73               | 1.170(1.065-1.286) | 0.001         | NA            | NA             |
| 5                    | 5             | 820              | 1.681(1.104-2.560) | 0.015         | 79.5%         | 0.001          |
| NOS score            |               |                  |             |               |               |                |
| ≤6                   | 5             | 602              | 1.343(0.868-2.082) | 0.188         | 69.5%         | 0.011          |
| >6                   | 5             | 776              | 1.579(1.123-2.221) | 0.009         | 85.6%         | <0.001         |

*a* Numbers of studies included in the meta-analysis  
*b* Number of patients of included studies  
NA: not available; OS: overall survival; HR: hazard ratio; 95%CI: confidence interval; P: p value of pooled HR; F: value of Higgins I-squared statistics; Ph: p value of Heterogeneity test.
NLR and survival

There were 7 studies with multivariate analysis and 3 studies with univariate analysis providing information regarding OS. Overall, an elevated NLR was significantly associated with a poor OS (HR=1.48, 95%CI=1.16-1.89, P=0.001)(Figure 2). The significance was detected in studies with multivariate analysis (HR=1.50, 95%CI=1.15-1.95, P=0.003). We further detected a significant association between NLR and OS in studies with Caucasian population (HR=1.44, 95%CI=1.11-1.86, P=0.006), larger sample size (HR=1.58, 95%CI=1.07-2.35, P=0.022), higher study quality (HR = 1.579, 95%CI=1.12-2.22, P=0.009) and cut-off value of five (HR=1.68, 95%CI=1.10-2.56, P=0.015). The detailed results were shown in Table 2 and the extracted data were presented in Supplementary table S1.

NLR and clinical characteristics

As for clinical characteristics, we detected NLR level was associated with histology (odds ratio (OR)=0.59, 95%CI=0.40-0.86, P=0.005), patients with non-epithelioid histological subtype are more likely in an elevated NLR. However, we failed to observe the association between NLR level with gender, tumor stage and performance status (PS) score. These results were presented in Table 3 and detailed extracted data were shown in Supplementary table S2.

Sensitivity analysis and publication bias

Sensitivity analysis was performed and we did not observe any variations of the results, which proved the stability of results of our meta-analysis (Figure 3). In addition, The Begg’s funnel plot (Pr>|z|=0.474) (Figure 4a) and the Egger’s test (P>|t|=0.237) (Figure 4b) did not detected any evidence of publication bias for OS, as well as for clinical characteristics.

DISCUSSION

Systemic inflammatory response is important in cancer progression [33]. Inflammation-related cells involved in the constitution and regulation of tumor cell microenvironment. It may act as an intermediary between

Study ID | HR (95% CI) | Weight |
---|---|---|
Cedres (2014) | 0.84 (0.23, 3.06) | 2.85 |
Cihan (2014) | 0.70 (0.30, 1.80) | 4.96 |
Hooper (2015) | 1.17 (1.06, 1.29) | 15.14 |
Kao (2013) | 2.20 (1.38, 3.50) | 9.85 |
Kao (2011) | 1.79 (1.04, 3.07) | 8.73 |
Kao (2010) | 2.70 (1.80, 3.90) | 11.10 |
Meniawy (2013) | 1.01 (0.75, 1.36) | 12.55 |
Pinato (2012) | 2.00 (1.60, 3.20) | 11.76 |
Tanrikulu (2015) | 1.01 (0.74, 1.37) | 12.38 |
Yamagishi (2015) | 1.93 (1.28, 2.92) | 10.68 |
Overall (I²-squared = 78.3%, p = 0.000) | 1.48 (1.16, 1.89) | 100.00 |

NOTE: Weights are from random effects analysis

Figure 2: Forest plot of the association between NLR and OS in MPM overall. The elevated NLR was detected to be significantly associated with a poor OS. HR: hazard ratio; CI: confidence intervals.
tumor cell and inflammatory. Different peripheral blood count may reflect the body’s inflammatory response, and NLR as an combined index may reflect the balance between neutrophils and immunocytes, making it a prognostic factor. Several studies have demonstrated that elevated NLR is related with a poor prognosis in MPM, but the result still controversial. Thus we conducted this meta-analysis and it was the first to indicate that a high NLR was associated with poor survival of patients with MPM.

Table 3: The pooled data on clinical characteristics of included studies

| Variables       | N² | Case² | OR(95%CI)       | P    | F² | Ph |
|-----------------|----|-------|-----------------|------|----|----|
| Gender          | 3  | 488   |                 |      |    |    |
| Male            |    |       | Reference       |      |    |    |
| Female          |    |       | 0.793(0.516-1.219) | 0.290 | 0.0% | 0.369 |
| Histology       | 4  | 526   |                 |      |    |    |
| Epithelial      |    |       | Reference       |      |    |    |
| Non-epithelial  |    |       | 0.588(0.404-0.855) | 0.005 | 37.3% | 0.188 |
| Stage           | 2  | 205   |                 |      |    |    |
| I/II            |    |       | Reference       |      |    |    |
| III/IV          |    |       | 0.677(0.342-1.339) | 0.262 | 0.0% | 0.521 |
| PS score        | 2  | 302   |                 |      |    |    |
| 0               |    |       | Reference       |      |    |    |
| ≥1              |    |       | 0.652(0.379-1.120) | 0.121 | 0.0% | 0.410 |

^a Numbers of studies included in the meta-analysis

^b Number of patients of included studies

PS score: performance status score; OR: odds ratio; 95%CI: confidence interval; P: p value of pooled HR; F: value of X² based I-squared statistics; Ph: p value of Heterogeneity test.

Figure 3: Sensitivity analysis of included studies to evaluate the stability of our results. We did not observe any variations of the results, which proved the stability of results of our meta-analysis.
Figure 4: Begg’s funnel plot (a) and Egger’s linear regression tests (b) for the assessment of potential publication bias.
We did not detect any evidence of publication bias for OS.
Similar to our study, a recent clinical research published in 2016 investigated the relation between NLR and malignant pleural mesothelioma [22]. In their research they collected and analysed 36 patients’ clinical information, and didn’t detect any significant correlation between NLR and MPM prognosis. Thus we could find that NLR on prognosis of patients with malignant pleural mesothelioma was still a question worth exploring. These studies just as we mentioned above, might not be able to draw reliable conclusions with the limitation of sample size. Our research using the method of meta-analysis contained a larger sample size, and might be more credible and provide more reliable information compared to other single clinical research.

In conclusion, our study demonstrated that the elevated NLR predicted poor survival of MPM. And NLR also might be associated with histology of MPM. The NLR could be useful for predicting survival of patients with MPM. Further studies were warranted to conform the exact value of NLR in the prognosis of MPM.

MATERIALS AND METHODS

Search strategy

A systemic search was conducted in PubMed, Embase and web of Science databases update to Jun 26, 2016. The following words were applied as search terms: “neutrophil-to-lymphocyte”, “neutrophil-lymphocyte ratio”, “neutrophil/lymphocyte ratio”, “NLR”, “malignant pleural mesothelioma”, “malignant mesothelioma”, “pleural mesothelioma”, “MPM”, “MM”. There was no language restriction of our literature search. The references of identified articles were retrieved manually for potential eligible studies.

Inclusion and exclusion criteria

Studies met the following criteria were considered eligible: (1) the studies investigated the association between NLR and prognosis or clinical characteristics of MPM patients; (2) for prognosis, hazard ratio (HR) and 95% CI were reported, or Kaplan-Meier curve and relevant information were available to estimate HR and 95% CI. (3) for clinical characteristics, odds ratio (OR) and 95% CI were used to measure the association. We excluded studies if they: (1) were conference abstracts, letters, case reports; (2) failed to report failed to present specific NLR data for OS in neither univariate nor multivariate analysis, or failed to estimate via sufficient information for HR and 95% CI, or NLR as a continue variable; (3) presented to be duplicate publications. When studies with overlapping
patients were met, only the study with the most patients was included. Two investigators (Nan Chen and Shuai Liu) reviewed the identified studies independently and a final discussion was launched to reach a consistency.

Data extraction and quality assessment

Two investigators (Nan Chen and Lin Huang) extracted information independently using a standard data extraction table. The following information were recorded for each included study: name of first author, year of publication, ethnicity, number of recruited patients, treatment of patient, follow-up time, analysis method, type of survival, cut-off value for NLR, clinical characteristics information, HR and 95% CI for survival. The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the quality of each included study independently by these two investigators. NOS score more than 6 were considered as high-quality studies. The two investigators discussed to reach a consensus when there was any disagreement. The Newcastle-Ottawa Quality Assessment Scale (NOS) we used was shown in Supplementary table S3 and the detailed scores of each included study was presented in Supplementary table S4.

Statistics analysis

In this meta-analysis, OR with 95%CI was used to evaluate the association between NLR and clinical characteristics. As for prognosis, HR and 95%CI were extracted from each study to calculate the pooled HR (high level vs. low level). When the study reported both univariate and multivariate results, we chose multivariate analysis for final calculation. While the HR and 95%CI were not reported directly, Kaplan-Meier curve and relevant data were collected to estimate related HR with 95%CI. Test of heterogeneity was conducted by Cochran’s Q test and Higgins I-squared statistic. P>0.10 and I2<50% were regarded as no significant heterogeneity and the fixed-effects model was used. Otherwise, the random-effects model was applied. In addition, further subgroup analyses to explore potential heterogeneity were performed stratified by ethnicity, sample size, study design, survival analysis, NOS score and cut-off value. We further conducted sensitivity to evaluate the stability of the results. Additionally, Begg’s funnel plot and Egger’s linear regression tests were performed to access publication bias. All the analyses were carried out by STATA 12.0 (STATA Corporation, College Station, TX, USA).

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CONFLICTS OF INTEREST

There is no conflict of interest.

REFERENCES

1. Vigneri P, Martorana F, Manzella F, Stella S. Biomarkers and prognostic factors for malignant pleural mesothelioma. Future Oncol. 2015; 29-33. doi:10.2217/fon.15.317.
2. Gill RR, Richards WG, Yeap BY, Matsuoka S, Wolf AS, Gerbaudo VH, Bueno R, Sugarbaker DJ, Hatabu H. Epithelial malignant pleural mesothelioma after extrapleural pneumonectomy: stratification of survival with CT-derived tumor volume. AJR Am J Roentgenol. 2012; 198: 359-63. doi: 10.2214/AJR.11.7015.
3. Francart J, Vaes E, Henrard S, Legrand C, Baas P, Gaafer R, van Meerbeeck JP, Sylvester R, Robert A. A prognostic index for progression-free survival in malignant mesothelioma with application to the design of phase II trials: a combined analysis of 10 EORTC trials. Eur J Cancer. 2009; 45: 2304-11. doi: 10.1016/j.ejca.2009.04.028.
4. Eiro N, Vizoso FJ. Inflammation and cancer. World J Gastrointest Surg. 2012; 4: 62-72. doi: 10.4240/wjgs.v4.i3.62.
5. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? The Lancet. 2001; 357: 539-45. doi: 10.1016/s0140-6736(00)04046-0.
6. Grange JM, Krone B, Mastrangelo G. Infection, inflammation and cancer. Int J Cancer. 2011; 128: 2240-1. doi: 10.1002/ijc.25533.
7. Moore MM, Chua W, Charles KA, Clarke SJ. Inflammation and cancer: causes and consequences. Clin Pharmacol Ther. 2010; 87: 504-8. doi: 10.1038/clpt.2009.254.
8. Grosse-Steffen T, Giese T, Giese N, Longerich T, Schirmacher P, Hansch GM, Gaida MM. Epithelial-to-mesenchymal transition in pancreatic ductal adenocarcinoma and pancreatic tumor cell lines: the role of neutrophils and neutrophil-derived elastase. Clin Dev Immunol. 2012; 2012: 720768. doi: 10.1155/2012/720768.
9. Zhang T, Guo W, Yang Y, Liu W, Guo L, Gu Y, Shu Y, Wang L, Wu X, Hua Z, Ke Y, Sun Y, Shen Y, et al. Loss of SHP-2 activity in CD4+ T cells promotes melanoma progression and metastasis. Sci Rep. 2013; 3: 2845. doi: 10.1038/srep02845.
10. Schwaller J, Schneider P, Mhawech-Fauceglia P, McKee T, Myit S, Matthes T, Tschopp J, Donze O, Gal FA, Huard B. Neutrophil-derived APRIL concentrated in tumor lesions by proteoglycans correlates with human B-cell lymphoma aggressiveness. Blood. 2007; 331-338. doi: 10.1182/blood2006-02-001800.
11. Schumacher D, Strilic B, Sivaraj KK, Wetschureck N, Offermanns S. Platelet-derived nucleotides promote tumor-cell transendothelial migration and metastasis via P2Y2 receptor. Cancer Cell. 2013; 24: 130-7. doi: 10.1016/j.
12. Keizman D, Ish-Shalom M, Huang P, Eisenberger MA, Pili R, Hammers H, Carducci MA. The association of pretreatment neutrophil to lymphocyte ratio with response rate, progression free survival and overall survival of patients treated with sunitinib for metastatic renal cell carcinoma. Eur J Cancer. 2012; 48: 202-8. doi: 10.1016/j.ejca.2011.09.001.

13. Zhou D, Zhang Y, Xu L, Zhou Z, Huang J, Chen M. A monocyte/lymphocyte ratio predicts survival in patients with hepatocellular carcinoma. Sci Rep. 2015; 5: 15263. doi: 10.1038/srep15263.

14. Guthrie GJ, Roxburgh CS, Farhan-Alanie OM, Horgan PG, McMillan DC. Comparison of the prognostic value of longitudinal measurements of systemic inflammation in patients undergoing curative resection of colorectal cancer. Br J Cancer. 2013; 109: 24-8. doi: 10.1038/bjc.2013.330.

15. Oh BS, Jang JW, Kwon JH, You CR, Chung KW, Kay CS, Jung HS, Lee S. Prognostic value of C-reactive protein and neutrophil-to-lymphocyte ratio in patients with hepatocellular carcinoma. BMC Cancer. 2013; 13:78. doi:10.1186/1471-2407-13-78.

16. Sharaia RZ, Halazun KJ, Mirza F, Port JL, Lee PC, Neugut AI, Altorki NK, Abrams JA. Elevated preoperative neutrophil:lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer. Ann Surg Oncol. 2011; 18: 3362-9. doi: 10.1245/s10434-011-1754-8.

17. Gu X, Gao X, Li X, Qi X, Ma M, Qin S, Yu H, Sun S, Zhou D, Wang W. Prognostic significance of neutrophil-to-lymphocyte ratio in prostate cancer: evidence from 16,266 patients. Sci Rep. 2016; 6: 22089. doi: 10.1038/srep22089.

18. Yamanaka T, Matsumoto S, Teramukai S, Ishiwata R, Nagai Y, Fukushima M. The Baseline Ratio of Neutrophils to Lymphocytes Is Associated with Patient Prognosis in Advanced Gastric Cancer. Oncology. 2007; 73: 215-20. doi: 10.1159/000127412.

19. Ghanim B, Klikovits T, Hoda MA, Lang G, Szirtes I, Setinek U, Rozsas A, Renyi-Vamos F, Laszlo V, Grusch M, Filipits M, Scheed A, Jakopovic M, et al. K667 index is an independent prognostic factor in epithelial but not in non-epithelial malignant pleural mesothelioma: a multicenter study. Br J Cancer. 2015; 112: 783-92. doi: 10.1038/ bjc.2015.9.

20. Cedres S, Montero MA, Martinez P, Martinez A, Rodriguez-Freixinos V, Torrejon D, Gabaldon A, Salcedo M, Ramon YC, Felip E. Exploratory analysis of activation of PTEN-P13K pathway and downstream proteins in malignant pleural mesothelioma (MPM). Lung Cancer. 2012; 77: 192-8. doi: 10.1016/j.lungcan.2012.02.022.

21. Kao SC, Vardy J, Harvie R, Chatfield M, van Zandwijk N, Clarke S, Pavlakis N. Health-related quality of life and inflammatory markers in malignant pleural mesothelioma. Support Care Cancer. 2013; 21: 697-705. doi: 10.1007/ s00520-012-1569-6.

22. Tural Onur S, Sokucu SN, Dalar L, Iliaz S, Kara K, Buyukkale S, Altim S. Are neutrophil/lymphocyte ratio and platelet/lymphocyte ratio reliable parameters as prognostic indicators in malignant mesothelioma? Ther Clin Risk Manag. 2016; 12: 651-6. doi: 10.2147/TCRM.S104077.

23. Abakay O, Tanrikulu AC, Palanci Y, Abakay A. The value of inflammatory parameters in the prognosis of malignant mesothelioma. J Int Med Res. 2014; 42: 554-65. doi: 10.1177/0300060513504163.

24. Cedres S, Montero MA, Zamora E, Martinez A, Martinez P, Farinas L, Navarro A, Torrejon D, Gabaldon A, Ramon YC, Felip E. Expression of Wilms’ tumor gene (WT1) is associated with survival in malignant pleural mesothelioma. Clin Transl Oncol. 2014; 16: 776-82. doi: 10.1007/s12094-013-1146-6.

25. Cihan YB, Ozturk A, Mutlu H. Relationship Between Prognosis and Neutrophil: Lymphocyte and Platelet: Lymphocyte Ratios in Patients with Malignant Pleural Mesotheliomas. Asian Pacific Journal of Cancer Prevention. 2014; 15: 2061-7. doi: 10.7314/ apjcp.2014.15.5.2061.

26. Hooper CE, Lyburn ID, Searle J, Darby M, Hall T, Hall D, Morley A, White P, Rahman NM, De Winton E, Clive A, Masani V, Arnold DT, et al. The South West Area Mesothelioma and Pemetrexed trial: a multicentre prospective observational study evaluating novel markers of chemotherapy response and prognostication. Br J Cancer. 2015; 112: 1175-82. doi: 10.1038/bjc.2015.62.

27. Kao SC, Vardy J, Chatfield M, Corte P, Pavlakis N, Clarke C, van Zandwijk N, Clarke S. Validation of prognostic factors in malignant pleural mesothelioma: a retrospective analysis of data from patients seeking compensation from the New South Wales Dust Diseases Board. Clin Lung Cancer. 2013; 14: 70-7. doi: 10.1016/j.clcc.2012.03.011.

28. Kao SC, Klebe S, Henderson DW, Reid G, Chatfield M, Armstrong NJ, Yan TD, Vardy J, Clarke S, Zandwijk N, McCoagham B. Low calretinin expression and high neutrophil-to-lymphocyte ratio are poor prognostic factors in patients with malignant mesothelioma undergoing extrapleural pneumonectomy. J Thorac Oncol. 2011; 1923-329. doi: 10.1097/JTO.0b013e31822a3740.

29. Kao SC, Pavlakis N, Harvie R, Vardy JL, Boyer MJ, van Zandwijk N, Clarke SJ. High blood neutrophil-to-lymphocyte ratio is an indicator of poor prognosis in malignant mesothelioma patients undergoing systemic therapy. Clin Cancer Res. 2010; 16: 5805-13. doi: 10.1158/1078-0432.CCR-10-2245.

30. Meniawy TM, Creaney J, Lake RA, Nowak AK. Existing models, but not neutrophil-to-lymphocyte ratio, are prognostic in malignant mesothelioma. Br J Cancer. 2013; 109: 1813-20. doi: 10.1038/bjc.2013.504.

31. Pinato DJ, Maur FA, Ramakrishnan R, Wahab L, Lloyd T, Sharma R. Inflammation-based prognostic indices in malignant pleural mesothelioma. J Thorac Oncol. 2012; 587-94. doi: 10.1097/JTO.0b013e31823f45c1.
32. Yamagishi T, Fujimoto N, Nishi H, Miyamoto Y, Hara N, Asano M, Fuchimoto Y, Wada S, Kitamura K, Ozaki S, Kishimoto T. Prognostic significance of the lymphocyte-to-monocyte ratio in patients with malignant pleural mesothelioma. Lung Cancer. 2015; 90: 111-7. doi: 10.1016/j.lungcan.2015.07.014.

33. Candido J, Hagemann T. Cancer-related inflammation. J Clin Immunol. 2013; 33: S79-84. doi: 10.1007/s10875-012-9847-0.

34. Xue TC, Zhang L, Xie XY, Ge NL, Li LX, Zhang BH, Ye SL, Ren ZG. Prognostic significance of the neutrophil-to-lymphocyte ratio in primary liver cancer: a meta-analysis. PLoS One. 2014; 9: e96072. doi: 10.1371/journal.pone.0096072.

35. Li MX, Liu XM, Zhang XF, Zhang JF, Wang WL, Zhu Y, Dong J, Cheng JW, Liu ZW, Ma L, Lv Y. Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. Int J Cancer. 2014; 134: 2403-13. doi: 10.1002/ijc.28536.

36. Cheng H, Long F, Jaiswar M, Yang L, Wang C, Zhou Z. Prognostic role of the neutrophil-to-lymphocyte ratio in pancreatic cancer: a meta-analysis. Sci Rep. 2015; 5: 11026. doi: 10.1038/srep11026.

37. Graziosi L, Marino E, De Angelis V, Rebonato A, Cavazzoni E, Donini A. Prognostic value of preoperative neutrophils to lymphocytes ratio in patients resected for gastric cancer. Am J Surg. 2015; 209: 333-7. doi: 10.1016/j.amjsurg.2014.06.014.