The Applicability of Neutrophil-Lymphocyte Ratio in Predicting The Survival of Nasopharyngeal Cancer: An Evidence Based Case Report
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Abstract

Background. Nasopharyngeal cancer (NPC) is still a huge burden especially in distinct parts of the world where it has high prevalence and mortality. There are several prognostic factors in NPC, however additional marker is needed to give a better picture on disease outcome. Innate and adaptive immunity play a great role in disease progression; however, the role of neutrophil-lymphocyte ratio (NLR) is still controversial. This study aimed to investigate the role of NLR status as a prognostic factor in NPC.

Methods. Literature search was conducted through PubMed, Cochrane, ProQuest, EBSCO and Science Direct following specific keywords. Duplicates were filtered out and remaining articles were screened based on the eligibility criteria before critical appraisal and measurement of level of evidence by The Centre for Evidence-Based Medicine (CEBM) University of Oxford. Review for the best available evidence was done by two-independent reviewer.

Result. : 130 records were retrieved and 6 final articles were selected for final appraisal. All studies were published after 2017 with sample sizes ranging from 140 to 5973 subjects. NLR cut-offs varied across studies (2.21-3.6) and the overall survival (OS) ranging from 51-82.5%. Moreover, 5-year disease specific survival (DSS) and progression free survival (PFS) for low and high NLR were 76-90.5% vs 53-82.1% and 68-86.2% vs 52-76.5%, respectively.

Conclusion. NLR status can be used to predict OS in NPC patients. A careful approach should be taken in determining treatment options. Further research is needed to understand the role of NLR in combination with other biomarker to predict the survival of NPC patients.

Keywords: Neutrophil-Lymphocyte Ratio, Nasopharyngeal Cancer, Survival.

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Introduction

In 2018, a total of 129,079 cases of nasopharyngeal cancer (NPC) were reported globally. NPC is particularly endemic in East and South East parts of Asia; Indonesia recorded 17,992 cases of NPC in 2018. Moreover, NPC caused 72,987 deaths worldwide and Indonesia has one of the highest mortality rate (11,204 deaths) along with lower quality of life among its patients. Therefore, further actions should be done to counteract and prevent the impact that may be caused by NPC.

Currently, radiotherapy with or without chemotherapy is the mainstay treatment for NPC. Additional induction or adjuvant chemotherapy may be given; however, the risks and benefits should be thoroughly considered before giving further aggressive treatment. Among prognostic factors that are known to affect the survival of NPC patients, TNM staging is widely used to predict the course of disease. Nevertheless, TNM staging alone is insufficient and other biomarkers are rapidly emerging and widely available markers in predicting the prognosis of NPC. Both inflammation and immune response play essential parts in NPC disease progressivity and prognosis. This process may be affected by several inflammatory cells, such as neutrophils and lymphocytes. In the tumor microenvironment, neutrophils play a great role in the promotion of tumor growth, invasion, angiogenesis and metastasis. On the contrary, studies on lymphocytes resulted in the anti-tumor response which will mediate tumor rejection and growth suppression through various immunological pathway. Studies showed that neutrophil-lymphocyte ratio (NLR) has the potential to be a prognostic marker for
various cancer types. However, its role in predicting the outcome of NPC patients and its applicability in developing countries, such as Indonesia, is still unknown. This evidence-based case report aimed to elucidate the role of NLR as a prognostic factor, primarily overall survival (OS) and subsequently secondary survival outcomes such as 5-year disease specific survival (DSS) and progression free survival (PFS).

**Case Illustration**
A 65-year-old male came to a radiation oncologist with the chief complaint of frequent nosebleeds (epistaxis), about 3 to 4 times a week, and a progressive headache. Physical examination showed no lymph node enlargement and cranial nerve palsy but trismus was found. On CT-scan examination, there was a solid mass on the posterolateral, particularly on the right side of the nasopharynx which obliterated bilateral pharyngeal recesses, torus tubarius, tensor veli palatini muscle, splenius capitis muscle, and longus capitis muscle. The mass also extended to the posterior nasal cavity and right maxillary sinus. There was also enlargement of the left level II lymph node. No abnormality was found on the chest X-Ray, abdominal ultrasound and bone scan. The histopathology examination corresponded with non-keratinizing squamous cell carcinoma. Based on these examinations, this patient was diagnosed with NPC T2N1M0 (stage II) and was planned to have chemo radiation therapy (CRT). However, the patient was concerned about his life expectancy. Knowing that staging and metastasis alone is not sufficient to predict the prognosis and cancer is commonly related to the inflammatory reaction inside the body, the doctor found that simple inflammatory marker such as NLR can give additional information on the survivorship of the NPC patients.

**Methods**
Literature search was done through five different electronic databases (PubMed, Cochrane, ProQuest, EBSCO and Science Direct). Keywords of (“Nasopharyngeal carcinoma” OR “Nasopharyngeal cancer” OR “Nasopharyngeal neoplasm” OR NPC) AND (“Neutrophil-to-lymphocyte ratio” OR “Neutrophil-lymphocyte ratio” OR NLR OR RNL) were used during the search carried out on April 8th 2019 (Table 1).

Duplicates were filtered out and the remaining articles were screened based on eligibility criteria before the assessment of full-texts was conducted. Inclusion criteria used in this report were clinical/observational studies, systematic review/meta-analysis, studies consisted of all stage of nasopharyngeal cancer patients, written in English or Indonesian language, studies which measured pre-treatment NLR and overall survival as study outcome. Studies were excluded if there were no full text available or if the study population was children (≤ 19 years old).

| Electronic Database | Keywords | Hits | Articles included |
|---------------------|----------|-----|-------------------|
| PubMed              | (((((nasopharyngeal carcinoma[Title/Abstract]) OR nasopharyngeal cancer [Title/Abstract]) OR NPC[Title/Abstract]) AND (((Neutrophil-lymphocyte ratio[Title/Abstract]) OR Neutrophil-to-lymphocyte ratio[Title/Abstract]) OR NLR[Title/Abstract]) OR RNL[Title/Abstract]) | 35 | 6 |
| Cochrane            | (nasopharyngeal carcinoma OR nasopharyngeal cancer OR nasopharyngeal neoplasm):ti,ab,kw AND (NLR OR RNL OR Neutrophil-lymphocyte ratio OR Neutrophil-to-lymphocyte ratio):ti,ab,kw | 3 | 0 |
| ProQuest            | (“Nasopharyngeal carcinoma” OR “Nasopharyngeal cancer” OR “Nasopharyngeal neoplasm” OR NPC) AND (“Neutrophil-to-lymphocyte ratio” OR “Neutrophil-lymphocyte ratio” OR NLR OR RNL) | 8 | 3 |
| EBSCO               | (“Nasopharyngeal carcinoma” OR “Nasopharyngeal cancer” OR “Nasopharyngeal neoplasm” OR NPC) AND (“Neutrophil-to-lymphocyte ratio” OR “Neutrophil-lymphocyte ratio” OR NLR OR RNL) | 79 | 6 |
| Science Direct      | (“Nasopharyngeal carcinoma” OR “Nasopharyngeal cancer” OR “Nasopharyngeal neoplasm” OR NPC) AND (“Neutrophil-to-lymphocyte ratio” OR “Neutrophil-lymphocyte ratio” OR NLR OR RNL) | 5 | 0 |

*Duplicates were filtered out, 6 final articles were included in critical appraisal
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Selected articles were appraised by using critical appraisal tools from The Centre for Evidence-Based Medicine (CEBM) University of Oxford. Level of evidence was measured by using "Oxford Center for Evidence Medicine 2011 Level of Evidence". The criteria of validity, importance and applicability were reviewed by two-independent reviewer to select the best available evidence suitable with the clinical question.

Results
Literature Search
Five electronic databases searches resulted in 130 records. After removing duplicates and excluding 84 irrelevant/overlapping articles, 6 final articles consisting of 1 meta-analysis and 5 cohort studies were included for the critical appraisal. Nine articles were excluded because they were already included in a meta-analysis. Out of 5 systematic reviews/meta-analysis (SR/MA), only 1 meta-analysis was appraised. Four SR/MA were excluded due to the inclusion of other types of cancer, not suitable with eligibility criteria or was already included in Takenaka et al. Additional exclusion were made for 6 full-text articles because there was no clear analysis of the relationship between NLR and OS.

Characteristic of Studies
All studies were published after 2017, with level of evidence ranging from level 1 to 2, were conducted in Asia (predominantly in China) and with sample sizes varying from 140 to 5973 subjects. The included stages were mixed metastatic and non-metastatic diseases in three studies and only non-metastatic disease in two studies. The end-point analysed from these studies were OS and PFS in 6 studies, DMFS in 2 studies and DSS in 2 studies. Male and older adult subjects predominated in most studies.
| Author            | Aim                                                                 | Endpoints                                      | Study Design       | Samples and Other Remarks                                                                 | Result                                                                 | Conclusion                                                                 | Level of evidence |
|-------------------|----------------------------------------------------------------------|-----------------------------------------------|-------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------------|
| Liao et al., 2017 | To know how NLR affect prognosis in NPC                             | OS, PFS and DFS                               | Retrospective cohort conducted at Taiwan | 180 patients with histologically proven NPC (stage I-IV) treated at Far Eastern Memorial Hospital | Median follow up times: 4.4 years                                        | High NLR may independently affect survival for NPC patients. This effect is more prominent in advanced stages. | 2                  |
|                   |                                                                      |                                               |                   | Male 80%                                                                                   | 5-year OS (NLR <3.6 vs ≥3.6): 74 vs 51% (p = 0.022)                      |                                                                           |                                                                |
|                   |                                                                      |                                               |                   | Age < 65 years: 91.7%                                                                      | 5-year DSS (NLR <3.6 vs ≥3.6): 76 vs 53% (p = 0.011)                     |                                                                           |                                                                |
|                   |                                                                      |                                               |                   | Treatment:                                                                                 | 5-year PFS (NLR <3.6 vs ≥3.6): 68 vs 52% (p = 0.286)                     | HR for OS of NLR≥ 3.6: 2.76 (95%CI: 1.34-5.68), p= 0.01                 |                                                                |
|                   |                                                                      |                                               |                   | • Stage I treated by radiotherapy only                                                       | NLR cut-off was determined from previous study                           |                                                                           |                                                                |
|                   |                                                                      |                                               |                   | • Stage II-IVa received concurrent chemoradiotherapy (CCRT)                                 |                                                                         |                                                                           |                                                                |
|                   |                                                                      |                                               |                   | • Stage IVa-IVb induction chemotherapy followed CRT                                         |                                                                         |                                                                           |                                                                |
| Lu et al, 2017    | To evaluate the role of NLR, LMR, PLR in predicting survival and clinicopathology in NPC patients. | OS and PFS                                   | Retrospective cohort | 140 NPC patients admitted to Wuzhou Red Cross Hospital from Feb 2009 to May 2010 who were clinically staged (I-IVa) according to Chinese 2008 staging system and received radical therapy. | Median follow up = 68 months (5-77 months)                               | NLR measured before treatment was an independent prognostic factor in NPC and may be complementary to TNM staging in predicting survival of NPC patients. | 2                  |
|                   |                                                                      |                                               |                   | Age ≥ 45 years: 61%; Male: 72%;                                                            | 5-year OS (NLR <2.28 vs ≥2.28): 87.8 vs 70.3%, (p = 0.010)              |                                                                           |                                                                |
|                   |                                                                      |                                               |                   | Stage III-IVa: 86%                                                                          | 5-year PFS (NLR <2.28 vs ≥2.28): 86.2 vs 66.8%, (p = 0.005)             |                                                                           |                                                                |
|                   |                                                                      |                                               |                   | Treatment: Radiotherapy alone or combination of radiotherapy and chemotherapy                | HR for PFS of NLR≥ 2.28: 2.615 (95% CI 1.206-5.672), p=0.015            |                                                                           |                                                                |
| Ye et al, 2018    | To evaluate the prognostic values of hematological biomarkers in NPC patients receiving definitive intensity-modulated radiotherapy (IMRT) | OS and PFS                                   | Retrospective cohort | 427 NPC patients without distant metastasis treated with IMRT between January 2010 and March 2013 | Median follow-up = 67.5 months (4.8-85.5) months                        | Although NLR was a strong prognostic factor in NPC patients, it might not help determining the selection of treatment options for loco-regionally advanced NPC | 2                  |
|                   |                                                                      |                                               |                   | Male: 71.9%; Age: 48 years (17-82);                                                        | 5-year OS (NLR <2.32 vs ≥2.32): 90.0 vs 81.8%, (p = 0.015)              |                                                                           |                                                                |
|                   |                                                                      |                                               |                   | Stage III-IV: 79.2%                                                                        | 5-year PFS (NLR <2.32 vs ≥2.32): 81.5 vs 70.9%, (p = 0.005)             |                                                                           |                                                                |
|                   |                                                                      |                                               |                   | Treatment: Radiotherapy alone (IMRT) or combined chemoradiotherapy                          | HR for OS of NLR≥ 2.32: 1.699 (95% CI 1.005-2.873), p=0.048            |                                                                           |                                                                |
| Yao et al, 2019   | To evaluate the prognostic value of NLR in patients with NPC based on a large-scale cohort from an endemic area. | OS, DMFS, PFS                                | Retrospective cohort | 1550 NPC patients stage II-IV treated by radiotherapy with curative intent from October 2009 to August 2012 | Median follow-up duration: 54.3 months (IQR, 1.3–85.6 months)           | In advanced stage of NPC, high pretreatment NLR may be independently detrimental to survival. | 2                  |
|                   |                                                                      |                                               |                   | Median age: 45 (14-78) years; Male: 75.3%; Stage III-IVA-B: 78.5%                           | 5-year OS (NLR ≤2.50 vs > 2.50): 90.3 vs 82.5%; p <0.001              |                                                                           |                                                                |
|                   |                                                                      |                                               |                   | Treatment according to 7th edition of the AJCC staging system: IMRT and CCRT with/without neoadjuvant and adjuvant chemotherapy for stages III to IVB NPC | 5-year DMFS (NLR ≤2.50 vs > 2.50): 89.4 vs 85.0%; p =0.014            |                                                                           |                                                                |
|                   |                                                                      |                                               |                   |                                                                                           | 5-year PFS (NLR ≤2.50 vs > 2.50): 80.9 vs 76.5%; p = 0.031             |                                                                           |                                                                |
|                   |                                                                      |                                               |                   |                                                                                           | HR for OS of NLR >2.50: 1.68 (95% CI: 1.28-2.19)                         |                                                                           |                                                                |
|                   |                                                                      |                                               |                   |                                                                                           | NLR cut-off was determined by ROC                                         |                                                                           |                                                                |

**Table 2.** Characteristics of the included studies.
To evaluate the significance of pretreatment COP-NLR with the prognosis of IMRT-treated NPC patients

Lin et al, 2017\textsuperscript{13}

| 3-year DSS, LRFS, FFS, OS | Retrospective study in Kaohsiung Veterans General Hospital, Taiwan, Republic of China | 232 stage I to 4 NPC patients treated with IMRT between January 2006 and February 2012. Age: 50.70±11.47; Male: 70.3%; Stage III-IV: 87.9% Treatment: Stage I and II: RT or CCRT Stage III and IVb: CCRT with/without induction or adjuvant chemotherapy | Mean follow-up was 55.19±29.37 months 3-year OS (NLR ≤ 2.23 vs >2.23): 86.5 vs 77.9% (p=0.069) 3-year LRFS (NLR ≤ 2.23 vs >2.23): 93.6 vs 86.8% (p=0.084) 3-year DMFS (NLR ≤ 2.23 vs >2.23): 91.6 vs 82.7% (p=0.054) 3-year DSS (NLR ≤ 2.23 vs >2.23): 90.5 vs 82.1% (0.056) NLR was determined using ROC |

To know the impact of NLR on prognosis of NPC

Primary outcome: OS Secondary outcome: DSS, PFS, DMFS

Meta-analysis

Nine studies with 5397 patients (stage non-metastatic and metastatic) conducted in 2011 to 2016

Median cutoff values for NLR: 3.6 (2.48-5). HR for OS in higher NLR: 1.51 (95%CI: 1.27-1.78), p<0.001 HR for OS in 3.6 vs <3.6: 1.585 (95%CI: 1.295-1.940), p<0.001 HR for DSS in higher NLR: 1.44 (95% CI: 1.22-1.71), p=0.001 HR for PFS in higher NLR: 1.53 (95%CI: 1.22-1.90), p=0.001 HR for DMFS in higher NLR: 1.83 (95%CI: 1.14-2.95), p=0.012

In NPC, NLR was significant to predict survival of patients. However, small effect was found on OS, DSS, DFS and DMFS

NLR status

Neutrophils and lymphocytes were counted using an automated hematology system in 3 studies but two studies did not mention the methods.\textsuperscript{5,7,8,15,16} In the meta-analysis, only one study mentioned using an automated hematology analyzer.\textsuperscript{12}

NLR cut-off varied across studies (2.21-3.6). Takenaka et al used the 80th percentile of NLR value (3.6) taken from Chua et al.\textsuperscript{12,21} The NLR cut-offs in 3 studies were determined using receiver operating characteristic (ROC) curve.\textsuperscript{7,8,15} Liao et al referred the NLR cut-off from other study.\textsuperscript{5,22} Meanwhile, Ye et al did not mention the method used to determine the NLR cut-off value.\textsuperscript{16}

NLR status and survival

All studies indicated that higher NLR was associated with worse OS regardless the cut-off value (ranging from 51%-82.5%), but outcomes varied between stages.\textsuperscript{5,7,8,15,16} Moreover, comparison between metastatic and non-metastatic disease (25.5 and 74.5%) resulted in a larger gap (23%) in 3-year OS.\textsuperscript{15} Nevertheless, the studies that involved advanced stage patients showed little difference (<10%) in 5-year OS.\textsuperscript{7,16} From the available data, we could only estimate the 95% CI in Lu et al.\textsuperscript{8} The difference of 3-year and 5-year-OS between high and low NLR ranged from 8.6% and 7.8% to 23%.\textsuperscript{5,7,8,15,16} Meta-analysis showed that hazard ratio (HR) for OS in subjects with higher NLR was 1.51 (95%CI: 1.27-1.78).\textsuperscript{12} Both 3-year and 5-year DSS in higher NLR group were worse than lower NLR group. The 3-year and 5-year DSS for low and high NLR were 90.5 vs 82.1% and 76% vs 53%, respectively.\textsuperscript{5,15} Meanwhile, 5-year PFS was ranging from 52-76.5%. The 5-year-PFS difference between low vs high NLR ranged from 4.4% to 16%.\textsuperscript{5,7,8,16} The pooled HR for DSS and PFS in higher NLR was 1.44 and 1.53.\textsuperscript{12}

Discussion

In terms of validity, all 5 cohort studies retrospectively recruited patients who were newly diagnosed with NPC and allowed samples for NLR to be taken before antitumor treatment began.\textsuperscript{5,7,8,15,16} Follow-up was long enough to know the OS between stages but studies on NLR did not demonstrate sufficient follow-up period as
most of them failed to reach median survival.\textsuperscript{5}

Various stages of NPC were included in all studies, including metastatic diseases, as commonly seen in daily practice.\textsuperscript{5,7,15} The 7th edition AJCC (American Joint Committee on Cancer) staging system was used in 3 studies to determine staging of NPC.\textsuperscript{5,15,16} The later studies from 2019 used the 8th AJCC staging system which claimed to provide better segregation between clinical stage for long-term OS compared to the 7th edition.\textsuperscript{8,23} The Chinese 2008 staging system was used by Liao et al but was comparable to the 7th AJCC in regards to survival curves for 5-year OS.\textsuperscript{5,24} The value of NLR is known to be relatively proportional to the clinical stage of cancer (particularly to T and N staging) although it has been stated in research that the relationship is not always interdependent.\textsuperscript{8,25} To tackle the bias caused by variety in cancer stage and other prognostic factors, 3 studies underwent multivariate analysis for important variables.\textsuperscript{5,8,16} All of studies did not apply “blinding” in measuring the end-point since the outcome was objective. The best available evidence was the meta-analysis by Takenaka et al which stated that HR for OS in subjects with elevated NLR is 1.51.\textsuperscript{12} Although this study did not search on gray literature, the result was precise given the narrow and significant 95% CI. Moreover,

| Study | Validity | Importance | Applicability |
|-------|----------|------------|--------------|
| Liao et al, 2017\textsuperscript{5} | Yes | No | Yes | Yes | 5-year OS (NLR <3.6 vs ≥3.6): 74 vs 51% (p = 0.022) | N/A | No | Yes |
| Lu et al, 2017\textsuperscript{8} | Yes | No | Yes | Yes | 5-year OS (NLR <2.28 vs ≥2.28): 87.8% vs 70.3%, (p = 0.010) | OS for NLR ≥2.28: 70.3%; 95%CI: 59.8-80.8% | No | Yes |
| Ye et al, 2018\textsuperscript{16} | Yes | No | Yes | Yes | 5-year OS (NLR <2.32 vs ≥2.32): 90.0% vs 81.8%, (p = 0.015) | N/A | No | Yes |
| Yao et al, 2019\textsuperscript{7} | Yes | No | Yes | No | 5-year OS (NLR ≤2.50 vs > 2.50): 90.3 vs 82.5% (p =0.001) | N/A | No | Yes |
| Lin et al, 2017\textsuperscript{15} | Yes | No | Yes | No | 3-year OS (NLR ≤ 2.23 vs >2.23): 86.5 vs 77.9% (p=0.069) | N/A | No | Yes |

*OS, PFS and DMFS definition are different between studies; N/A: no data available on number of patients with high and low NLR

| Study | Validity | Importance | Applicability |
|-------|----------|------------|--------------|
| Takenaka et al, 2017\textsuperscript{12} | Yes | Yes | Yes | Yes | Yes | HR for OS in higher NLR: 1.51 (95%CI: 1.27-1.78), p=0.001 |

Heterogeneity:
Q value=0.316, p value= 0.676, I\textsuperscript{2}: 0%
the effect was homogenous across studies for OS, PFS and DSS (p value for Cochrane Q >0.05; I² < 4%). The effect of increased NLR on OS was relatively smaller than other biomarker such as pretreatment and posttreatment EBV DNA (HR 2.78 and 5.43).26 Combination of other biomarker such as platelet counts (COP) might enhance the predicting ability of NLR yet lead to underestimation of NLR impact to prognosis.15 The inconsistency of the NLR cut-off values among individual studies should be faced with careful consideration in clinical practice. Limited amount of studies hinder meta-regression analysis to determine the optimal cut-off value.12 The cut-off value of 5 showed highest HR in the prognosis of solid tumors.27 However, emerging studies dating from 2017 used, on average, a lower cut-off:5,7,8,15,16

NLR is a simple and cost-effective examination with the approximate price of 120,000 IDR. Measurement of complete blood count is almost mandatory for pretreatment evaluation in cancer patients. Therefore, it does not add extra effort for both patients and doctors to gain extra value from routine laboratory test. In some developing countries, such as Indonesia, complete blood count test is covered by national health insurance, allowing for repeated measurements. We recommend doctors to order complete blood count (including differential count) before treatment and calculate the NLR that might be useful for explaining patient's survival. In our case, the early-stage cancer combined with NLR value of 2,4 (% neutrophil count:65, % lymphocyte count: 26,4) might indicated favourable outcome if appropriate and timely treatment is applied. Yet, it should not be independently used to determine treatment options (less aggressive vs more aggressive). Using a scoring system generated from multiple prognostic factors might be a more careful approach to this case. Further research, especially in developing countries, should be conducted to investigate the association between each stage, NLR (including the combination with other biomarkers) and survival of patients.

Conclusion

NLR status can be used to predict overall survival in NPC patients. Although NLR independently affected the survival of NPC patients, a careful approach should be taken in regards of determining treatment options. Further research is needed to know the role of NLR in combination with other biomarker to yield the best scoring system in predicting the survival of patients.

Conflicts of Interest

None declared.

References

1. Chua MLK, Wee JTS, Hui EP, Chan ATC. Nasopharyngeal carcinoma. Lancet Lond Engl. 2016 Mar 5;387(10022):1012–24.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
3. GLOBOCAN. Nasopharynx cancer [Internet]. International Agency for Research on Cancer-World Health Organization. 2018 [cited 2019 Feb 13]. Available from: gco.iarc.fr
4. Jang-Chun L, Jing-Min H, Yee-Min J, Dai-Wei L, Chang-Ming C, Chun-Shu L, et al. Comparisons of quality of life for patients with nasopharyngeal carcinoma after treatment with different RT technologies. Acta Otorhinolaryngol Ital Organo Uff Soc Ital Otorinolaringol E Chir Cerv-facc. 2014;34(4):241–6.
5. Liao LJ, Hsu WL, Wang CT, Lo WC, Cheng PW, Shuang PW, et al. Prognostic impact of pre-treatment neutrophil-to-lymphocyte ratio (NLR) in nasopharyngeal carcinoma: A retrospective study of 180 Taiwanese patients. Clin Otolaryngol. 2018;43(2):463–9.
6. Ng WT, Chang ATY, Lee SWM, Sze HCK, Lee AWM. Chemotherapy for nasopharyngeal cancer: Neoadjuvant, concomitant, and/or adjuvant. Curr Treat Options Oncol. 2015 Sep 19;16(9):44.
7. Yao JJ, Zhu FT, Dong J, Liang Z Bin, Yang LW, Chen SY, et al. Prognostic value of neutrophil-to-lymphocyte ratio in advanced nasopharyngeal carcinoma: A large institution-based cohort study from an endemic area. BMC Cancer. 2019;19(1):1–8.
8. Lu A, Li H, Zheng Y, Tang M, Li J, Wu H, et al. Prognostic significance of neutrophil to lymphocyte ratio, lymphocyte to monocyte ratio, and platelet to lymphocyte ratio in patients with nasopharyngeal carcinoma. BioMed Res Int. 2017;2017:1–6.
9. Sadcalan DB, Lucero JA, Sadcalan DL. Prognostic utility of baseline neutrophil-to-lymphocyte ratio in patients receiving immune checkpoint inhibitors: A review and meta-analysis. OncoTargets Ther. 2018;11:955–65.
10. Mizuno R, Kawada K, Itatani Y, Ogawa R, Kiyasu Y, Sakai Y, et al. The role of tumor-associated neutrophils in colorectal cancer. Int J Mol Sci. 2019 Jan 27;20(3):529.
11. Ostroumov D, Fekete-Drimusz N, Saborowski M, Kühnel F, Woller N. CD4 and CD8 T lymphocyte interplay in controlling tumor growth. Cell Mol Life Sci. 2018;75(4):689–713.
12. Takenaka Y, Kitamura T, Oya R, Ashida N, Shimizu K, Takemura K, et al. Prognostic role of neutrophil–lymphocyte ratio in nasopharyngeal carcinoma: A meta-analysis. PLoS ONE. 2017;12(7):1–12.
13. Centre for Evidence-Based Medicine-University of Oxford. Critical appraisal tools - CEBM [Internet]. [cited 2019 Apr 13]. Available from: https://www.cebm.net/2014/06/critical-appraisal/
14. The Centre for Evidence-Based Medicine - University of Oxford. OCEBM Levels of Evidence - CEBM [Internet]. [cited 2019 Apr 13]. Available from: https://www.cebm.net/2016/05/ocebm-levels-of-evidence/
15. Lin YH, Chang KP, Lin YS, Chang TS. Pretreatment combination of platelet counts and neutrophil-lymphocyte ratio predicts survival of nasopharyngeal cancer patients receiving intensity-modulated radiotherapy. OncoTargets Ther. 2017;10:2751–60.
16. Ye L, Oei RW, Kong F, Xu T, Shen C, Wang X, et al. Prognostic values of hematological biomarkers in nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy. Eur Arch Otorhinolaryngol. 2018;275(5):1309–17.
17. Su L, Zhang M, Zhang W, Cai C, Hong J. Pretreatment hematologic markers as prognostic factors in patients with nasopharyngeal carcinoma: A systematic review and meta-analysis. Medicine (Baltimore). 2017 Mar 1;96(11):e6364.
18. Yin J, Qin Y, Luo YK, Feng M, Lang JY. Prognostic value of neutrophil-to-lymphocyte ratio for nasopharyngeal carcinoma. Med U S. 2017;96(29).
19. Yu B, Li Z, Zheng Q, Luo Z, Li J, Zhou Y, et al. Prognostic value of neutrophil to lymphocyte ratio in patients with nasopharyngeal carcinoma: A meta-analysis. Biomed Res. 2017;28(3):1378-82.
20. Dolan RD, Laird BJA, Horgan PG, McMillan DC. The prognostic value of the systemic inflammatory response in randomised clinical trials in cancer: A systematic review.
21. Chua MLK, Tan SH, Kusumawidjaja G, Shwe MTT, Cheah SL, Fong KW, et al. Neutrophil-to-lymphocyte ratio as a prognostic marker in locally advanced nasopharyngeal carcinoma: A pooled analysis of two randomised controlled trials. Eur J Cancer. 2016;67:119–29.
22. Jin Y, Ye X, He C, Zhang B, Zhang Y. Pretreatment neutrophil-to-lymphocyte ratio as predictor of survival for patients with metastatic nasopharyngeal carcinoma. Head Neck. 2015 Jan 1;37(1):69–75.
23. Yang X-L, Wang Y, Liang S-B, He S-S, Chen D-M, Chen H-Y, et al. Comparison of the seventh and eighth editions of the UICC/AJCC staging system for nasopharyngeal carcinoma: analysis of 1317 patients treated with intensity-modulated radiotherapy at two centers.
24. Pan J, Xu Y, Qiu S, Zong J, Guo Q, Zhang Y, et al. A comparison between the Chinese 2008 and the 7th edition AJCC staging systems for nasopharyngeal carcinoma. Am J Clin Oncol. 2015 Apr 1;38(2):189–96.
25. Liew KY, Zulkiflee AB. Neutrophil-lymphocyte ratios in the prognostication of primary non-metastatic nasopharyngeal carcinoma. Braz J Otorhinolaryngol. 2018;84(6):764-771.
26. Zhang J, Shu C, Song Y, Li Q, Huang J, Ma X. Epstein-Barr virus DNA level as a novel prognostic factor in nasopharyngeal carcinoma: A meta-analysis. Medicine (Baltimore). 2016 Oct 1;95(40):e5130.
27. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, et al. Prognostic Role of neutrophil-to-lymphocyte ratio in solid tumors: A systematic review and meta-analysis. J Natl Cancer Inst. 2014;106(6):dj4124.