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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.

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.[1,2] 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.[3,4] 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.[5] Additional induction or adjuvant chemotherapy may be given; however, the risks and benefits should be thoroughly considered before giving further aggressive treatment.[6] 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.[5,7]

Both inflammation and immune response play essential parts in NPC disease progressivity and prognosis.[8,9] This process may be affected by several inflammatory cells, such as neutrophils and lymphocytes.[5] In the tumor microenvironment, neutrophils play a great role in the promotion of tumor growth, invasion, angiogenesis and metastasis.[10] On the contrary, studies on lymphocytes resulted in the anti-tumor response which will mediate tumor rejection and growth suppression through various immunological path-way.[5,11]

Studies showed that neutrophil-lymphocyte ratio (NLR) has the potential to be a prognostic marker for

various cancer types.[12] 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 chemoradiotherapy (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).

Table 1. Search strategy.

Electronic Database	Keywords	Hits	Articles included*
PubMed	(((((nasopharyngeal carcinoma[Title/Abstract]) OR nasopharyngeal cancer [Title/Abstract]) OR nasopharyngeal neoplasm[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-lymphocte 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

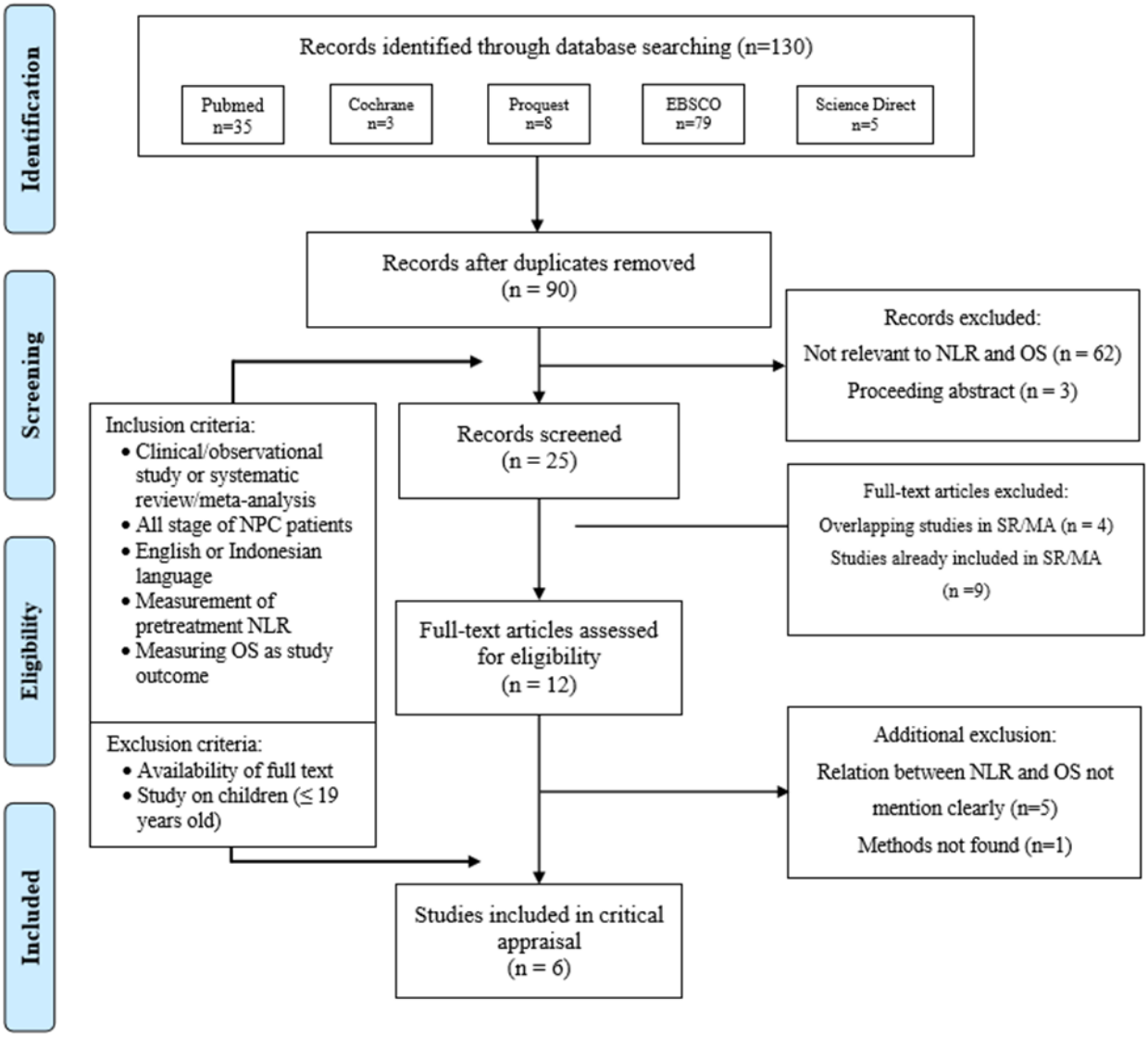

Figure 1. Flowchart of search strategy.

Selected articles were appraised by using critical appraisal tools from The Centre for Evidence-Based Medicine (CEBM) University of Oxford.[13] Level of evidence was measured by using "Oxford Center for Evidence Medicine 2011 Level of Evidence".[14] 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.[5,7,8,12,15,16] 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.[12,17–20] 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[5,7,12,15] and only non-metastatic disease in two studies[8,16]. The end-point analysed from these studies were OS and PFS in 6 studies, DMFS in 2 studies[7,12] and DSS in 2 studies[12,15]. Male and older adult subjects predominated in most studies.

Table 2. Characteristics of the included studies.

Author	Aim	End-points	Study Design	Samples and Other Remarks	Result	Conclusion	Level of evidence
Liao et al, 2017[5]	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 Male 80%; Age < 65 years: 91.7% Treatment: • Stage I treated by radio-therapy only • Stage II-IVa received concurrent chemoradio-therapy (CCRT) • Stage IVa-IVb induction chemotherapy followed CCRT	Median follow up times: 4.4 years 5-year OS (NLR <3.6 vs ≥3.6): 74 vs 51% (p = 0.022) 5-year DSS (NLR <3.6 vs ≥3.6): 76 vs 53% (p = 0.011) 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 NLR cut-off was determined from previous study	High NLR may independently affect survival for NPC patients. This effect is more prominent in advanced stages.	2
Lu et al, 2017[8]	To evaluate the role of NLR, LMR, PLR in predicting survival and clinico-pathology 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. Age ≥ 45 years: 61%; Male: 72%; Stage III-IVa: 86% Treatment: Radiotherapy alone or combination of radiotherapy and chemotherapy	Median follow up = 68 months (5-77 months) 5-year OS (NLR <2.28 vs ≥2.28): 87.8 vs 70.3%, (p = 0.010) 5-year PFS (NLR <2.28 vs ≥2.28): 86.2 vs 66.8%, (p = 0.005) HR for PFS of NLR≥ 2.28: 2.615 (95% CI 1.206-5.672), p= 0.015 NLR cut-off was determined using ROC	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
Ye et al, 2018[16]	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 Male: 71.9%; Age: 48 years (17-82); Stage III-IV: 79.2% Treatment: Radiotherapy alone (IMRT) or combined chemora-diotherapy	Median follow-up = 67.5 (4.8-85,5) months 5-year OS (NLR <2.32 vs ≥2.32): 90.0 vs 81.8%, (p = 0.015) 5-year PFS (NLR <2.32 vs ≥2.32): 81,5 vs 70,9%, (p = 0.005) HR for OS of NLR≥ 2.32: 1.699 (95% CI 1.005-2.873), p= 0.048 NLR cut-off method not mentioned	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
Yao et al, 2019[7]	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 age: 45 (14-78) years; Male: 75.3%; Stage III-IVA-B: 78.5% 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	Median follow-up duration: 54,3 months (IQR, 1.3–85.6 months) 5-year OS (NLR ≤2.50 vs > 2.50): 90.3 vs 82.5%; p <0.001 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	In advanced stage of NPC, high pretreatment NLR may be independently detrimental to survival.	2

Table 2. (continued).

Lin et al, 2017[15]	To evaluate the signifi-cance of pretreatment COP-NLR with the prognosis of IMRT-treated NPC patients	3-year DSS, LRFS, FFS, OS	Retrospective study in Kaohsiung Veterans General Hospital, Taiwan, Republic of China	232 stage 1 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	NLR alone is insufficient to predict survival. Combination of platelet count and neutrophil-lymphocyte ratio (COP-NLR) predicted a better survival of NPC patients.	2
Takenaka et al, 2017[12]	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 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	1

NLR status

Neutrophils and lymphocytes were counted using an automated hematology system in 3 studies but two studies did not mentioned the methods.[5,7,8,15,16] In the meta-analysis, only one study mentioned using an automated hematology analyzer.[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.[12,21] The NLR cut-offs in 3 studies were determined using receiver operating characteristic (ROC) curve.[7,8,15] Liao et al referred the NLR cut-off from other study.[5,22] Meanwhile, Ye et al did not mention the method used to determine the NLR cut-off value.[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.[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.[15] Nevertheless, the studies that involved advanced stage patients showed little difference (<10%) in 5-year OS.[7,16] From the available data, we could only estimate the 95% CI in Lu et al.[8] The difference of 3-year and 5-year-OS between high and low NLR ranged from 8.6% and 7.8% to 23%.[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).[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.[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%.[5,7,8,16] The pooled HR for DSS and PFS in higher NLR was 1.44 and 1.53.[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.[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

Table 3. Critical appraisal for selected cohort studies (n = 5).

Study	Validity				Importance		Applicability	
	Patients assembled at a common point	Sufficiently long and complete follow-up	Objective or "blind" outcome	Adjustment for important prognostic factor	Outcomes over time	Prognostic estimates	Different patient characteristic	Clinically important
Liao et al, 2017[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[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[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[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[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

most of them failed to reach median survival.[5]

Various stages of NPC were included in all studies, including metastatic diseases, as commonly seen in daily practice.[5,7,15] The 7th edition AJCC (American Joint Committee on Cancer) staging system was used in 3 studies to determine staging of NPC.[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.[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.[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.[8,25] To tackle the bias caused by variety in cancer stage and other prognostic factors, 3 studies underwent multivariate analysis for important variables.[5,8,16] All of studies did not applied "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.[12] Although this study did not search on gray literature, the result was precise given the narrow and significant 95% CI. Moreover,

Table 4. Critical appraisal for meta-analysis (n = 1).

Study	**Validity**					**Importance**	Applicability	
	Focused question	Any important studies missed?	Appropriate inclusion criteria	Validity appraisal of included studies	Similarity of results	Overall results	Clinically important	Benefits over harm and cost
Takenaka et al, 2017[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^2: 0%	Yes	Yes

the effect was homogenous across studies for OS, PFS and DSS (p value for Cohrane 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.

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