

Original Research Article

Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio and one year survival of lung cancer in Sanglah hospital

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ABSTRACT

Background: Lung cancer is ranked third as the most common cancer in Indonesia. The one-year survival rate of advanced-stage non-small cell lung carcinoma (NSCLC) patient is quite low, that is 24.6%. Effective and inexpensive prognostic markers need to be further studied due to an increasing incidence of cancer. Inflammation plays an important role in tumorigenesis and research showed an association of NLR and PLR values with poor prognosis in patients with various solid tumors, but current cut off values still vary. This study wanted to determine the value of NLR, PLR and their relationship with the survival rate of advanced stage NSCLC patients at Sanglah hospital.

Methods: A retrospective cohort study using the medical record of 96 advanced-stage NSCLC patients who underwent treatment since January 2018 in Sanglah hospital, was closely monitored for a year since diagnosed. Analysis was performed with ROC, Kaplan Meier analysis, log rank test, and time independent cox regression model.

Results: The one-year survival rate of advanced stage NSCLC patient is 14.6%, with median survival 3.26 months. Cut off NLR > 3.37, median survival 2.66, p=0.00. Cut off PLR > 178.55, median survival 3.26, p=0.35. Multivariate analysis showed that NLR, HR=2.75 and performance status, HR=1.78 were associated with survival.

Conclusions: NLR with cut off >3.37 is associated with one-year survival rate of advanced-stage NSCLC patient. PLR did not have any significant association with one-year survival rate of advanced-stage NSCLC patient.

Keywords: Cut off, NLR, PLR, Survival, Lung cancer

INTRODUCTION

Lung cancer is the leading cause of cancer death in America, and in 2019 there were an estimated 228,150 new cases with an estimated lung cancer death of 142,670 and only 18% of patients with lung cancer survive within five years of being diagnosed.¹ Non-Small cell lung carcinoma (NSCLC) is 80% of all lung cancers and NSCLC has a better prognosis than Small Cell Lung Cancer (SCLC).¹ Data from Dharmais hospital shows that lung cancer is the third most common cancer after breast

and cervical cancer. The incidence of new cases also increased by 45% in 3 years with a mortality rate of 32% in 2010 and 37.5% in 2013.² The prognosis of NSCLC patients is quite poor and studies at RSCM and Dharmais hospital from 2007 to 2013 showed that stage IIB and IV NSCLC patients who survived the first year were only 24.6%.³ It is known that one-year survival shows a significant relationship with overall survival in patients with NSCLC.⁴ The survival of patients with advanced NSCLC varies but shows better rates in Asians than non-Asians, at this time data on the survival of patients with advanced stage NSCLC in Bali are not available.⁵

Determining which cancer patients can pass the first year, is still a complicated problem but needs to be done so that medical personnel can provide education, information and treatment plan to patients. Treatment options in advanced cancer are limited with some side effects, and the greatest expenditure for lung cancer occurs in the first 6 months after diagnosed.⁶ Determining factors related to the patient's prognosis is important, especially in patients with advanced cancer. Treatment of patients should not cause a worse effect on patients and should not waste resources and facilities that are limited in developing countries and should adjusted to patient's prognosis.

The role of inflammation is very important in tumorigenesis and the tumor microenvironment, which is largely maintained by inflammatory cells, an integral part of the malignancy process. Several prognostic markers are being studied, and in patients with advanced lung cancer, more attention is focusing to the role of immunology, particularly with the development of immune checkpoint inhibitors as a first-line treatment strategy. Several immunological markers have begun to be studied in patients with NSCLC but most of these markers are difficult to do and relatively expensive, especially in developing countries, which have relatively large number of cases. Routine blood test are test that are easy, inexpensive, and can be carried out by most health facilities in developing countries, these tests can provide information about the value of neutrophils, lymphocytes and platelets. Inflammatory parameters of the blood, neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) is reported to have a role in predicting the prognosis of patients with solid tumors.^{7,8} Several studies on solid tumors have shown an association between NLR and PLR with poor prognosis in patients with multiple metastatic solid tumors. There are strong evidence that an increased risk of death from cancer is associated with high NLR and PLR values. NLR and PLR may be used as prognostic markers of various solid tumors in clinical practice.^{8,9} Effective and inexpensive prognostic markers need to be investigated for widespread use in dealing with the increasing incidence of cancer. Currently, the cut off points of NLR and PLR related to the prognosis of solid cancer patients are still varies in various studies on solid tumor prognosis.^{7,8,10,11} Sanglah hospital, Bali as a cancer center in eastern Indonesia currently does not have data on the NLR and PLR of patients with advanced stage NSCLC, and its relationship with the survival of patients with NSCLC. This study are expected to be able to assist clinicians in estimating the survival of advanced stage NSCLC.

METHODS

The research was conducted at Sanglah hospital, Denpasar Bali from January to December 2020. This is an analytic observational study using a retrospective cohort design with 96 samples of advanced-stage NSCLC patients. The data was taken from the medical records of

outpatients and inpatients at Sanglah hospital Denpasar who were diagnosed with non-small cell lung cancer and received services at Sanglah hospital Denpasar Bali since January 2018 by consecutive sampling. Inclusion criteria were over 18 years of age and diagnosed with NSCLC, exclusion criteria are having metabolic disorders, diabetes militus and other malignancies besides lung cancer. The patient's neutrophil, lymphocyte, and platelet values at initial diagnosis and patient characteristics were recorded, then the patient's course was followed for 1 year or until the patient died. Research ethics and research permission are completed according to the provisions. The collected data was then processed for determination of AUC with ROC, Kaplan Meier analysis, log rank test, and time independent cox regression model using SPSS 20 statistical software

RESULTS

There were 96 samples with characteristic data as shown in (Tabel 1). The mean neutrophils were 10.09 (2.23-32.79), lymphocytes 1.82 (0.52-4.35), platelets 342.19 (122-702.50) while the average NLR was 7.00 (1.03-39.99), and the average PLR was 219.37 (53.97-748.50). One year survival patient with NSCLC was 14.6% with a median survival of 3.26 months (95% CI 1.24-5.28). The AUC value obtained from the ROC method was 86.6% (95% CI 79.6%-93.7%). The optimal cut point of the NLR value is obtained, which can be seen in (Figure 1).

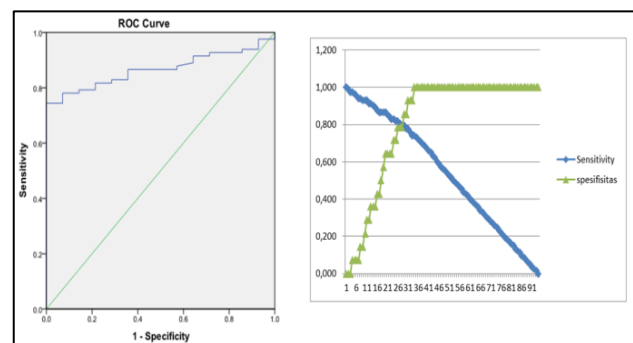


Figure 1: Receiver Operating Characteristic (ROC) curve of NLR and determination of NLR cut off point.

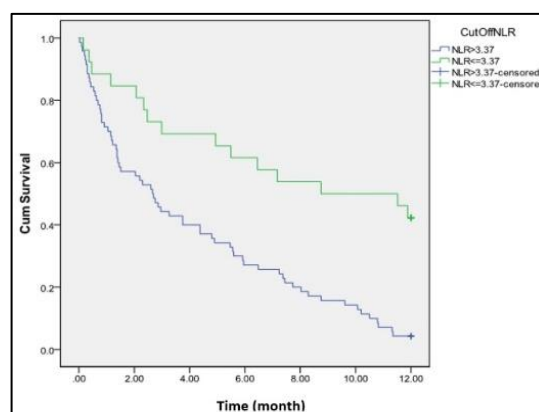


Figure 2: Kaplan Meier curve of NLR.

In this study, the optimal cut-off point for NLR was >3.37 (sensitivity 81.7% and specificity 78.6%). Median survival at NLR>3.37 was 2.66 months (95% CI 1.71-3.60), shorter compared to median survival at NLR ≤3.37 which was 8.75 months (95%CI 1.97-15.53) as shown in (Figure 2). Hazard ratio (HR) NLR>3.37 was 3.18 (95% CI 1.786–5.687) and statistically significant. The AUC value of PLR obtained from the ROC method was 62.7% (95% CI 48.4%-77.0%). the median survival at PLR>178.55 was 3.26 months (95%CI 1.31–5.21), shorter than the median survival at PLR≤ 78.55 which was 4.38 months (95%CI 0.744–8.02), p=0.35 (log rank) and statistically not significant, as shown in (Figure 3).

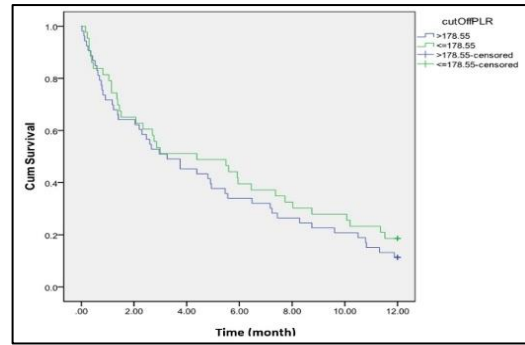


Figure 3: Kaplan Meier curve of PLR.

Table 1: Characteristics of advanced NSCLC subjects (N=96).

Variables	N (%)	Variables	N (%)
Status		Initial complaint	
Death	82 (85.4)	Chronic cough	38 (39.6)
Life	14 (14.6)	Coughing up blood	18 (18.8)
Gender		Shortness of breath	31 (32.3)
Man	61 (63.5)	Chest/back pain	6 (6.3)
woman	35 (36.5)	Neurological complaints	3 (3.1)
Age group (years)		Therapy	
>65	25 (26)	Chemotherapy	32 (33.3)
65	71 (74)	TKI	17 (17.7)
Work		Radiotherapy	4 (4.2)
Housewife	28 (29.2)	No therapy	43 (44.8)
Farmer	17 (17.7)	Type of chemotherapy (N=32)	
Construction workers	5 (5.2)	Paclitaxel carboplatin	13 (40.6)
Private employees	33 (34.4)	Pemetrexate carboplatin	12 (37.5)
Government employees	13 (13.5)	Paclitaxel cisplatin	1 (3.1)
Level of education		Vinorelbine carboplatin	2 (6.2)
Primary school	36 (37.5)	Pemetrexate cisplatin	3 (9.4)
Junior high school	12 (12.5)	Gemcitabine carboplatin	1 (3.1)
Senior high school	30 (31.3)	Lung tumor location	
Bachelor/diploma	9 (9.4)	Right	65(67.7)
No school	9 (9.4)	Left	29(30.2)
Smoking behavior		Both lungs	2 (2.1)
Smoker	53 (55.2)	Pleural effusion	
Non smoker	43 (44.8)	Right	29 (30.2)
Tumor type		Left	19 (19.8)
NSCLC	10 (10.4)	Bilateral	6 (6.3)
Squamous cell lung carcinoma	21 (21.9)	No pleural effusion	42 (43.8)
Adenocarcinoma	65 (67.7)	Performance status	
How to make a diagnosis		ECOG >2	30 (31.3)
Bronchoscopy	16 (16.7)	ECOG ≤2	66 (68.8)
Transthoracic biopsy	56 (58.3)		
Open biopsy	12 (12.5)		
FNAB	6 (6.3)		
effusion cytology	6 (6.3)		

The median survival and log rank values of each variable are shown in (Table 2), and it can be seen that NLR, performance status, tumor type and treatment type had

statistically significant differences in median survival. Multivariate analysis of the variables that met the proportional assumption and the bivariate analysis had p value <0.25 indicating the variables associated with

patient mortality were NLR ($p=0.01$, HR=2.75 95% CI 1.52-4.98) and performance status ($p=0.17$, HR=1.78 (95% CI 1.11-2.86)).

Table 2: Median survival and log rank test.

Variable	Median survival	Lower	Upper	Rank Log
NLR				
>3.37	2.66	1.71	3.60	0
≤3.37	8.75	1.97	15.53	
PLR				
>178.55	3.26	1.31	5.21	0.350
≤178.55	4.38	0.744	8.02	
Gender				
Man	3.75	1.45	6.05	0.641
Woman	2.96	0	6.58	
Age (years)				
>65	3.75	1.01	6.49	0.616
65	3.21	1.12	5.41	
Smoking behavior				
Smoker	4.38	2.20	6.56	0.692
Non smoker	2.86	0.87	4.85	
Performance status				
ECOG >2	0.82	0.60	1.03	0.000
ECOG ≤2	5.49	4.35	6.63	
Lung tumor type				
NSCLC	2.60	0.55	4.65	0.018
Squamous cell carcinoma	2.99	0.00	6.25	
Adenocarcinoma	4.38	1,244	5.28	
Type of therapy				
No Therapy	1.15	0.59	1.70	0.000
Radiotherapy	11.32	-	-	
Chemotherapy	5.56	4.92	6.19	
TKI	10.82	8.87	12.77	

To determine the effect of other variables, a multivariate analysis was also carried out with survival cox regression analysis of the interaction model with variables that are theoretically important but do not meet the requirements for the assumption of PH, with the results are: interaction of type of therapy and performance status (no therapy with performance status ECOG>2), HR 7.929 (95% CI 4.212-14.925), interaction of age and performance status (age group >65 years with performance status ECOG >2), HR 5.648, (95% CI 1.968-16.208), interaction type of histology and performance status (NSCLC with performance status ECOG>2), HR 8,538 (95% CI 1.083-67.29), (squamous cell carcinoma with performance status ECOG>2), HR 3.00 (95% CI 1.328-6.777) were associated with one year survival in patients with advanced NSCLC.

DISCUSSION

The majority of subjects were male, and smoker with average age was 60.15 years. Based on radiological examination, 67.7% of lung masses were found in the right lung and pleural effusion was found in 56.2% of

patients and most of them were right pleural effusions similar with the study of Ramadhaniah.¹² Histological diagnosis lung adenocarcinoma was the most common diagnosis in this study, other studies have also shown that the most common type of histology is adenocarcinoma.^{3,12-15}

The initial performance status of patients in this study, 31.3% was ECOG>2, which indicates that patients should receive general improvement management before receiving therapy for their cancer. This is different from the research in Jakarta which showed that performance status of most sample was ECOG 2, and there was no sample with ECOG>2, with most of the patient education being high school, while in this study the level of education mostly elementary school.³ The level of education will influence the decision to seek health services.¹⁶ The lower the level of education, the later the patient will seek medical help so new patients usually come to the hospital when they are in poor condition or with poor performance status.

One year survival of advanced stage NSCLC was 14.6% with a median survival of 3.26 months (95% CI 1.24-5.28). This is shorter than the study at RSCM and Dharmais Hospital Jakarta which showed 34.8% survival at 1 year but the study covered all stages and not only advanced stages as in this study.¹⁵

In this study, the median survival was 1.15 months in the group that did not receive therapy, not much different from study in Jakarta which showed a median survival of 2 months.³

In this study, the hazard ratio (HR) of NLR>3.37 was 2.75 (95% CI 1.52-4.98) and was statistically significant. Other research showed different NLR cut-off points (2.48-5) with different HR (1.37-2.15) but all were statistically significant related to the survival of NSCLC patients as found in this study.^{10,13,17-21}

The results of this study confirm that NLR is significantly related to the survival of NSCLC patients. Neutrophil known to play a role in the oncogenesis stage so it reflects the development of cancer while lymphocytes reflect the body's efforts to suppress the oncogenesis process. An increase in neutrophils and a decrease in lymphocytes characterized by an increase in NLR indicates the progression of tumor cells and a decrease in the body's defense efforts to suppress tumor cells, thereby reducing the patient's survival. In this study, the intersection point PLR was >178.55 (sensitivity 57.3% and specificity 57.1%) the median survival at PLR >178.55 was 3.26 months (95%CI 1.31-5.21), shorter than the median survival at PLR≤178.55 which was 4.38 months (95%CI 0.744-8.02), p=0.35 (log rank) and statistically not significant. Other study also gave the same result.^{19,22} All studies that showing PLR does not have a significant relationship with the survival of NSCLC patients using samples of stage 4 cancer, same as this study.

Mehmet Kos' research in 2015 showed interesting results, the analysis at all stages of the NSCLC showed that the PLR cut point <198 was associated with survival HR 1.45 (1.04-2.32) but in the subgroup analysis it was found that patients with metastases did not have a statistically significant relationship with HR 1.30 (95% CI 0.70-2.40).²³ Several studies showed different results, PLR was associated with the survival of NSCLC patients and all studies used samples of patients with stage 1 to 4 NSCLC and not only advanced stages.^{21,24}

The studies shows that different results were obtained with different stages of the NSCLC sample used in the study. This may reflect the different roles of platelets in tumor cell growth, angiogenesis and metastases (cancer stage) stages. Research by Haryati in Banjarmasin in 2019 showed that there was an increase in NLR and PLR in the early and advanced stages of NSCLC but the difference in PLR in the early and advanced stages was not statistically significant (260 verses 343 p=0.39),

while the difference in NLR was statistically significant (3.86 vs 8.33 p=0.013).²⁵ A study by Siamack Sabrkhany showed that VEGF was significantly increased in the platelets of stage 1-2 and stage 3-4 patients while PDGF was only increased in stage 1-2 only.²⁶ Platelets and tumor cells influence each other and show a relationship called the platelet tumor loop.²⁷

Cancer cells can also exhibit platelet mimicry, tumor cells can express platelet and megakaryocyte-specific gene products that play a role in tumor growth, angiogenesis and metastasis. In addition to regulating angiogenesis, platelets also regulate vascular integrity, thereby preventing bleeding in tumors.²⁸ Platelets not only have a detrimental effect on cancer but also have a protective effect, but when platelets have a detrimental effect and when it have a protective effect require further research.²⁷

We also found that performance status was significantly associated with one-year survival of patients with advanced stage NSCLC. In addition, we wanted to see the effect of several variables that were theoretically important but did not meet the requirements for the assumption of proportional hazard on survival, so that an interaction model analysis was carried out and it was found that age, type of therapy, histological diagnosis of lung cancer also had an effect on one-year survival of patients with advanced stage NSCLC.

Limitations

The limitations of this study were it was a retrospective cohort study that relies on the completeness of the data contained in medical records, and not evaluate the length of time patients wait for diagnostics, the length of waiting for therapy, that may be related to patient survival. This study is the first study in Bali to examine the value of NLR, PLR and their relationship with one year survival in patients with advanced stage NSCLC.

CONCLUSION

NLR cut-off value >3.37 was significantly associated with one-year survival of advanced-stage NSCLC patients, while PLR did not have a significant relationship with one-year survival of advanced-stage NSCLC patients. Researchers suggest the use of NLR >3.37 as cut-off point in estimating the survival of advanced-stage NSCLC patients with HR 2.75 and carry out further research on the relationship between PLR and survival of NSCLC patients using various stages.

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