Neutrophil-to-lymphocyte ratio is modality to predict recurrence, disability and mortality of ischemic stroke following acute phase

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ABSTRACT

Stroke has been known as the second greatest cause of mortality and the third cause of disability. Ischemic stroke is more frequent than hemorrhagic stroke. The pathophysiology of ischemic stroke relates with inflammatory process. Neutrophil and lymphocyte are part of that process. Routine peripheral hematological laboratory, which contains information of neutrophil and lymphocyte, is easy, cheap and rapid test. This literature review purposes to explain the modality of neutrophil-lymphocyte ratio (NLR) in predicting the recurrence, disability and mortality of ischemic stroke following acute phase.

Keywords: disability, ischemic stroke, mortality, NLR, recurrence, stroke

INTRODUCTION

Stroke is a sudden neurological deficit which is caused by vascular and can be focally or globally (1). WHO reported that one of six people would have experience of stroke in their lifespan (2). Based on World Health Organization (WHO), the second-leading cause of death (75.2%) and the third-leading cause of disability (81%) are stroke. Mortality rate of stroke is higher in Asia and Indonesia is the second highest after Mongolia (3). Prevalence of stroke in Indonesia based on Indonesia's health research by the year 2018 is 10.9‰ and stroke is the major cause of disability (3,382.2/100,000 people-years) and mortality (193.3/100,000 people-years) in older adult (3,4).

Generally, there are two major classifications of stroke, such as ischemic stroke and hemorrhagic stroke. Ischemic stroke is infarction in focal cerebral, spinal, or retinal and cause episodic neurological dysfunction (5). Ischemic stroke is more frequently (80%) than hemorrhagic stroke. Subtype of ischemic stroke are classified by the etiology, such as cardioembolic, atherosclerosis, lacunar, un-

known cause and other cause of ischemic stroke (6). Diagnosis of ischemic stroke is made by clinical history, physical examination (including funduscopic examination) and radiographic imaging (Computed Tomography/CT-Scan, Magnetic Resonance Imaging/MRI, CT/MR angiography, transcranial doppler). Rarely, serum biomarker (S100 calcium binding protein B/S100B) and neuropathological evaluation are used in diagnosis of ischemic stroke (1).

The modality to assess disability of patient who suffered stroke is modified Rankin Scale (mRS). Score of mRS is divided into some categories, such as from 0 (no symptoms at all) to 5 (severe disability and always needs nursing care in all of their activity) and 6 being death (7).

Recurrent ischemic stroke means a recent neurological deficit of an existing deficit. The prevalence of recurrent ischemic stroke is higher in five years following ischemic stroke than two years following ischemic stroke (16% vs. 12.9%) (9,10). About 50% stroke patient who is more than 60 years old, have a higher chance of having recurrent stroke and male is more likely than female (10). There is an

approximately 38.7% patient of stroke do not control regularly (4). Irregular control is the main contribution of recurrent stroke besides metabolic diseases, such as diabetes mellitus, hypertension and obesity (10). The irregularly control fails to have proper secondary management. Therefore, it promotes the chance of having recurrent stroke. Furthermore, the recurrent ischemic stroke is caused by both irregularly control and various risk factors of stroke. Prevention of recurrent ischemic stroke depends on the management of the risk factors (9,10). Stroke survivor has limitation to do activity daily living (ADL) because alteration in mobility, behavior, emotion, and articulation. This limitation can be one of the recurrent stroke risk factors. Mortality and disability were more frequent in recurrent stroke group.

The pathophysiology of stroke is related with the complexity of inflammatory process and oxidative stress. There are many inflammatory mediators which play a key role in neutrophil infiltration to ischemic brain's neuron. In the other hand, leukocyte infiltration to the ischemic site is caused by chemokine's expression in endothelial cell (11). In the acute phase, high concentration of leukocyte in intravascular can correlate with the substantial of the infarction and severity of the ischemic brain, whereas low concentration of this blood component is associated with poorer prognosis in chronic phase (12).

NLR is prognosis predictor for heart failure, acute coronary syndrome, organ cancer, covid-19 and even in ischemic stroke. NLR is the proportion of neutrophil and lymphocyte count (13-17). Recently, NLR can be used to predicting the recurrence of ischemic stroke. This inexpensive, rapid and universal laboratory test as peripheral hematological test (such as, hemoglobin, leukocyte, platelet, and differential white cell count (neutrophil, lymphocyte, monocyte, basophil, eosinophil) is routinely checked, especially in emergency room (12). Therefore, this review aims to outline the modality of NLR ratio in predicting the recurrence, disability and mortality of ischemic stroke following acute phase.

NLR AND RECURRENT ISCHEMIC STROKE

Ischemic stroke is tightly related with the process of atherosclerosis. Inflammation has played a major role in forming atherosclerosis besides having risk factors and family history. Inflammation process can be detected by peripheral hematology laboratory test. It is inexpensive laboratory test and routinely checked (13). Leucocyte exhibits the incidence of recurrent ischemic stroke. However, there are various subtypes of leucocyte, such as neutro-

phil, lymphocyte, monocyte, basophil and eosinophil, which results to lower the sensitivity and specificity of leukocyte. NLR is more sensitive to predict the recurrence rate of ischemic stroke than leucocyte or neutrophil solely (14). Suh reported that the highest predictive value of recurrent ischemic stroke is NLR if compared to other components, as well as white blood cell (WBC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (15). In addition, chronic ischemic stroke patient has two fold higher risk of getting recurrent ischemic stroke which is detected in MRI (8). A China experiment reported that NLR was independent predictor of recurrent ischemic stroke in acute setting. Furthermore, NLR >3 had higher chance to have recurrent ischemic stroke event asides from stroke severity and poor prognosis (HR = 1.499; 95%CI; 1.161-1.935; p = 0.002) (13,21) .

There are many cut off variations to predict recurrent ischemic stroke. In China study, the cut off of NLR is 2.97, with 95% sensitivity and 53% specificity (22, 23). The other study, high score of mRS was found in NLR >4 (ORs/RRs = 3.469; 95%CI; 1.904-6.320) (19). In Turkey study, the cut off of NLR is 2.6 with high sensitivity and specificity (73% and 73% consecutively). This inconsistent and unstandardized cut off of NLR can be due to both insufficient and less variety of sample. Thus, further studies with bigger number of sample should be done to conclude a higher sensitivity and specificity and standardized cut off of NLR in predicting the recurrence rate of ischemic stroke (20).

Neutrophil is the first component of white blood cell (WBC) in vascular. It plays a key role in proinflammatory process and releasing proteolytic enzyme. Endothelial cell releases cytokines which elevate the upregulation of peripheral neutrophil. However, lymphocyte has a contrary effect with neutrophil in atherosclerosis (13,18,21). The high neutrophil and low lymphocyte amount in acute phase lead that NLR can be applied in acute phase to predict the recurrence rate of ischemic stroke (21).

Besides NLR, CRP is one of the inflammation indicators. There was a study which compared NLR and CRP in predicting mortality indicated that NLR was more associated with mortality in ischemic stroke (22). Furthermore, NLR and CRP also can predict the etiology of ischemic stroke. Both of NLR and CRP increase when the etiology of ischemic stroke are atherosclerosis and cardioembolic. Nevertheless, NLR is significantly higher in atherosclerosis than in cardioembolic as the etiology of stroke (23).

NLR is higher in female than male but insignificant. Inflammation maker is affected by estrogen

which extremely depends on age. Therefore, higher inflammation marker can be detected in peripheral blood laboratory in younger female (24).

Quan reported that high NLR had higher risk of recurrent stroke than low NLR in three month follow-up (OR = 1.8; p = < 0.0001; 95%CI; 1.476-2.350) and in one year follow-up (OR = 1.878; p = <0.0001; 95% CI; 1.546-2.281) (25). The other study showed that high NLR was significantly increasing the risk of recurrent ischemic stroke event (RR = 2.074; 95%CI; 1.485-2.896; p = < 0.001). The risk of recurrent ischemic stroke was increase when there were both high NLR and comorbid such as, hypertension, hyperlipidemia and current smoking (19).

NLR AND DISABILITY ISCHEMIC STROKE

Shi reported that NLR significantly correlated with disability of ischemic stroke patient after 3 month of acute ischemic stroke (OR = 1.17; 95%CI; 1.04-1.34; p = 0.024) (26). The other study concluded that moderate-severe disability could be related with high NLR (OR = 2.236; 95%CI; 1.472–3.397; p = < 0.001) (27). The higher NLR, the poorer outcome following acute ischemic stroke. In one study which divided mRS into 5 group showed that the increasing of NLR was significantly (p = 0.001) proportional with increasing the mRS (NLR = 3.99±0,12; mRS = 2 vs. NLR = 3.92±0.51; mRS = 3 vs. NLR = 4.1±0.93; mRS = 4 vs. NLR = 4.05±0.44; mRS = 5 vs. NLR = 5.95±0.39; mRS = 6) (28). Another study revealed that higher NLR was observed in poor outcome (mRS≥ 3) in 3 months following ischemic stroke (p = < 0.001) (29).

Qun reported that the cut-off of NLR which was significant to differentiate between good and poor outcome (p = <0.001; 95%CI; 0.77-0.81) was 2.9, with 75% sensitivity and 61% specificity (30). NLR≥ 2, which had high sensitivity and specificity (90% & 96%, consecutively) significantly had linked to unfavourable outcome (mRS ≥ 3) in 3 month after ischemic stroke (p = <0,001) (31). High score of mRS was found in NLR≥ 3.51 (95%CI = 0.727-0.825, p = <0.001). The sensitivity and specificity of NLR≥ 3.51 are 64.6% and 81.8%, respectively (32). The other study found that 35% ischemic stroke patient with NLR≥ 3 had moderate-severe disability. The cut-off of NLR which was described as unfavourable outcome was 2.39 with 72% sensitivity and 70.9% specificity (OR = 1.455; 95%CI; 1.083-1.956) (12). There was another study which exhibited that high NLR (NLR≥ 3) increased four times higher the risk of moderate-severe disability (mRS ≥ 3) with p = 0.006 (95%CI; 1.533-13.046) (18). A Korea study reported that NLR≥ 4.12 increased the risk of major disability with OR = 2.89 (p = 0.002; 95%CI; 1.62-5.12) (33). Song exhibited that high NLR linked with severe disability (ORs/RRs = 1.851; 95%CI = 1.325–

2.584; p = < 0.001). When NLR was high at two continuous days after stroke, it correlated with poor prognosis (ORs/RRs = 1.432; 95%CI; 1.266-1.619) (19). The other cut-off of NLR was 7 and related with poor outcome (mRS 4-6) (OR = 2.44; 95%CI; 1.73–3.42) (34). This is consistent with Hu, who reported that NLR ≥ 5.87 showed the poor outcome in 3 months after ischemic stroke (OR = 2.079; 95%CI; 1.232-3.506; p = 0.006) with 64.4% sensitivity and 59.2% specificity. The sensitivity and specificity could be increased by adding other parameters which were included in the risk factor of ischemic stroke (85.2% and 75.6%, respectively) (29). However, there was variety of cut-off between Asian and non-Asian population. The NLR was found higher in non-Asian population than in Asian population (9). In the other hand, the variety cut-off of NLR is affected with duration of the stroke. The longer the duration from stroke attack, the more optimal cut-off value to measure the outcome. A Turkey study reported that a significant increase of NLR was observed between admission and 24-hour post-ischemic stroke (3.58±2.4 to 7.04±5.1; p = <0.001) (35,40). Another study exhibited that NLR in the first 24 hours was slightly lower than in 48-72 hours after ischemic stroke (4.29 vs. 4.58). In addition, the specificity (66%) and sensitivity (76%) in 48-72 hours was also higher than in the first 24 hours (56% specificity and 55% sensitivity) after ischemic stroke. Furthermore, there were associations among NLR, the duration of stroke attack and disability in ischemic stroke patient. Patient with moderate-severe disability had higher NLR level than with mild disability in 24-48 hours of onset ischemic stroke (8.41±0.91 vs. 4.93±0.47; p = 0.001). Consistently, NLR level in moderate-severe disability was also higher than in mild disability in 48-72 hours of onset ischemic stroke (8.68±0.93 vs. 4.5±0.51; p = 0.009). This study showed that NLR≥ 4.58 had 5.58 times suffered moderate-severe disability than NLR≤ 4.58 (95%CI; 1.99-15.64, p = 0.001) (36) (Table 1).

NLR AND MORTALITY ISCHEMIC STROKE

CRP, which has been used as mortality predictor in cardiovascular disease, is inferior to NLR (15). Besides CRP, Fan investigated that routine hematologic parameters, such as NLR, which was an inexpensive, practical and objective test, correlated to mortality rate of ischemic stroke (37). NLR was higher in dead patients than in survive patients in ischemic stroke (p = 0.011) (38). One study exhibited that the level of NLR was higher in survive patients of ischemic stroke within 30 days than in dead patients (7.1 vs. 5.4; p = 0.005) (29). Shi reported that NLR linked with 3 months mortality rate following ischemic stroke (26). Other study from China showed

TABLE 1. The characteristics of NLR in ischemic stroke

Author	Year	Location	Age (years)	Predictive	Cut-off NLR	Sensitivity (%)	Specificity (%)	OR/RR/ HR	95% CI	*p*-value
Xue J,, et al. (12)	2017	China	61.8±10.2	Disability	2.39	72	70.9	1.455	1.083-1.956	0.013
		China		Recurrence	2.39	-	-	1.499	1.161-1.935	0.002
Angkananard T, et al. (16)	2018	Thailand	34.9-73.2	Recurrence	3.00	-	-	2.36	1.44-3.89	0.012
Sun G, et al. (17)	2020	China	47.72±11.94 79	Recurrence	2.97	95	53	2.457	1.096-5.508	0.03
Luo Y, et al. (18)	2020	China	62.7±10.5	Recurrence	2.94	69.6	77.1	4.502	0.691-0.843	<0.001
		China		Disability	3	-	-	4.502	1.533-13.046	0.006
Song SY, et al. (19)	2019	China	≥65	Recurrence	4	-	-	2.074	1.485-2.896	<0.001
		China		Disability	4	-	-	1.851	1.325-2.584	<0.001
		China		Mortality	4	-	-	1.220	1.105-1.347	<0.001
Köklü E, et al. (20)	2016	Turkey	60-76	Recurrence	2.6	73	71	7.779	3.685-16.424	0.001
Quan K, et al. (25)	2019	China	56-74	Recurrence	3	-	-	1.8	1.476-2.350	<0.0001
Shi J, et al. (26)	2018	China	68.1±12.0	Disability	3	-	-	1.17	1.04-1.34	0.024
		China		Mortality	3	-	-	1.42	1.22-1.72	<0.001
Cao X, et al. (27)	2020	China	66.81±12.58	Disability	3.23	59.1	70.4	2.236	1.472-3.397	<0.001
Tony AA, et al. (28)	2018	Egypt	62.64±10.99	Disability	3.92±0.51	-	-	-	-	0.001
		Egypt		Mortality	4.99	82.9	78.9	-	-	0.001
Hu Y, et al. (29)	2020	China	50-75	Disability and mortality	5.87	64.4	59.2	2.079	1.232-3.506	0.006
Qun S, et al. (30)	2017	China	69-72	Disability	2.995	75	61	2.547	0.77-0.81	<0.001
Elsheikh WM, et al. (31)	2020	Egypt	48-70	Disability	2.05	90	96	0.095	0.063-0.390	0.001
Chen C, et al. (32)	2021	China	66.8±12.2	Disability	3.51	64.6	81.8	2.32	0.727-0.825	<0.0001
Yu S, et al. (33)	2017	Korea	70.0±16.0	Disability	4.12	-	-	2.89	1.62-5.12	0.002
Duan Z, et al. (34)	2018	China	57-74	Disability	7	-	-	2.44	1.73-3.42	<0.001
				Mortality	5.9	-	-	6.69	1.7-26.3	<0.05
Bi Y, et al. (35)	2021	China	62-74	Mortality	3	-	-	1.71	1.01-2.42	<0.01
Petrone AB, et al. (36)	2019	USA	73±12	Disability	4.58	76	66	5.58	1.99-15.64	0.001
Malhotra K, et al. (39)	2018	USA	64.3±14.4	Mortality	2.2	51.4	63.1	1.56	1.08-2.24	0.018
Kozyolkin O, et al. (40)	2019	Ukraine	45-85	Mortality	4.8	80	86.5	1.11	1.00-1.21	0.0303

that NLR >3.23 was corelated with 90 days mortality following ischemic stroke (p = <0.001) (27). High NLR (≥ 4.12) has 2.61 times higher mortality rate than low NLR (≤ 4.12) (33). A study in USA reported that 3 month high-mortality rate was found in high NLR (p = 0.018) (39). Song demonstrated that the mortality rate had association with NLR level. The higher level of NLR linked with higher mortality rate in 30 days (HR= 1.220; 95%CI; 1.105–1.347; p = < 0.001), 60 days (HR= 3.300; 95%CI; 1.350-8.068; p = 0.009) and one year after 90 days follow-up (HR= 1.030; 95%CI; 1.010-1.050; p = 0.003) (19). Furthermore, high NLR also related with high mortality rate in recurrent ischemic stroke (40). This could be in consequence of chronic low-grade inflammatory circumstances in existing prior stroke. In addition,

it could be also caused by the rapid inflammatory response which was released when patient had recurrent stroke (25). NLR could be used to predict the lethal outcome at the time of admission with 80% sensitivity and 86.5% specificity (OR= 1.11; 95%CI; 1.00-1.21; p = 0.0303) (40). In Egypt study, NLR ≥ 4.99 could predict the mortality of ischemic stroke with high specificity and sensitivity (p = 0.001; 78.9% and 82.9%, respectively) (28). Moreover, NLR could be used to predict 3 month mortality rate in acute ischemic stroke. High NLR related with higher risk of 3 month mortality rate following acute ischemic stroke (95%CI; 1.01-2.42, p = < 0.01) (35). Malhotra reported that the cut-off of NLR, which associated with 3-month mortality rate, was 2.2. Patient who died 3 month after ischemic stroke had NLR >2.2 (P: 0.018) (39). The management of ischemic stroke as early prevention could decline the risk of mortality, which caused by ischemic stroke and adjust the NLR (35). The mortality rate also correlated with time of follow-up and NLR after ischemic stroke.

The association of NLR and mortality rate decreased overtime especially after two years follow-up. High NLR level has twice risk of dead in the first two years after ischemic stroke (41).

CONCLUSIONS

Besides CRP, WBC and other hematologic laboratory parameters, NLR is practical, rapid and inexpensive test, which have been used routinely checked. NLR has high sensitivity and specificity, which can be used to predicting the recurrence, disability, and mortality of ischemic stroke. High NLR correlates with high risk of recurrence, moderate-severe disability, and mortality rate of ischemic stroke. The cut-off of NLR is still very diverse. Therefore, further research with bigger number of sample requires to perform in order to obtain cut-off based on age, sex, comorbid, onset of stroke and other factors which can influence the level of NLR.

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