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C-reactive protein (CRP) and lactate dehydrogenase (LDH) as functional outcome predictors in stroke patients

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ABSTRACT

Stroke is a neurologic disorder with high mortality and disability. Its pathophysiology is associated with vascular inflammation. However, studies between vascular inflammatory markers and stroke outcomes are still limited. This study aimed to investigate the association between inflammatory markers and functional outcomes of stroke. This was a retrospective cohort study involving all stroke patients at the Dr. Sardjito General Hospital, Yogyakarta from October 2020 to August 2021 who meet the inclusion and exclusion criteria. Mann-Whitney was used for bivariate analysis, followed by multivariate analysis. A total of 269 subjects, with 213 infarcts (79.2%) and 56 hemorrhagic (20.8%) strokes. There were 83 subjects deceased (30.9%), with 66 infarct (31%) and 17 hemorrhagic (30.4%) strokes. High CRP levels had significant and independent associations with worse GCS, ADL, IADL, NIHSS, BI, SSGM, MRS, and higher mortality rates ($p < 0.05$). High LDH levels had a significant and independent association with worse GCS scores and higher mortality rates ($p < 0.05$). Sub-analysis showed high CRP and LDH had associations with high mortality rates in infarct ($p < 0.001$), but only CRP ($p = 0.029$) had associations with high mortality rates in hemorrhagic. There was no significant association between fibrinogen and procalcitonin with stroke outcomes ($p > 0.05$). Cox-regression analysis showed CRP>24.5 mg/dL and LDH >300U/L associated with hazard ratios of 3.2 ($p < 0.001$) and 1.65 ($p = 0.026$). In conclusion. high CRP and LDH levels are associated with mortality rates in stroke patients.

ABSTRAK

Stroke merupakan kelainan neurologis dengan angka kematian dan kecacatan tinggi. Patofisiologi stroke dikaitkan dengan peradangan pembuluh darah. Namun, penelitian antara penanda inflamasi vaskular dan luaran stroke masih terbatas. Penelitian ini bertujuan untuk mengkaji hubungan antara penanda inflamasi dan luaran fungsional stroke. Penelitian ini merupakan penelitian kohort retrospektif yang melibatkan seluruh pasien stroke di RSUP Dr. Sardjito Yogyakarta pada bulan Oktober 2020 hingga Agustus 2021 yang memenuhi kriteria inklusi dan eksklusi. Mann-Whitney digunakan untuk analisis bivariat, dilanjutkan dengan analisis multivariat. Sebanyak 269 subjek, dengan rincian 213 infark (79,2%) dan 56 stroke hemoragik (20,8%). Subjek meninggal dunia sebanyak 83 orang (30,9%), stroke infark sebanyak 66 orang (31%) dan stroke hemoragik sebanyak 17 orang (30,4%). Tingkat CRP yang tinggi memiliki hubungan yang signifikan dan independen dengan GCS, ADL, IADL, NIHSS, BI, SSGM, MRS yang lebih buruk, dan angka kematian yang lebih tinggi ($p <0,05$). Tingkat LDH yang tinggi memiliki hubungan yang signifikan dan independen dengan skor GCS yang lebih buruk dan angka kematian yang lebih tinggi ($p <0,05$). Sub-analisis menunjukkan CRP dan LDH yang tinggi berhubungan dengan tingkat kematian yang tinggi pada infark ($p <0,001$), namun hanya CRP ($p = 0,029$) yang memiliki hubungan dengan tingginya angka kematian pada hemoragik. Tidak terdapat hubungan bermakna antara fibrinogen dan prokalsitonin dengan luaran stroke ($p > 0,05$). Analisis regresi Cox menunjukkan CRP>24,5 mg/dL dan LDH >300U/L berhubungan dengan rasio bahaya sebesar 3,2 ($p < 0,001$) dan 1,65 ($p = 0,026$). Kesimpulannya, kadar CRP dan LDH yang tinggi berhubungan dengan angka kematian pada pasien stroke.

Keywords:
C-reactive protein; functional outcome; lactate dehydogenes; stroke

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INTRODUCTION

Stroke is a neurological disease with high morbidity and mortality.[1] World Stroke Organization reported 13.7 million new stroke cases and around 5.5 million deaths occur annually.[1] Approximately 87% of all deaths and disabilities due to stroke occur in low and middle-income countries. In Indonesia in 2018, the prevalence of stroke at the age of ≥15 y.o. was 10.9% or an estimated 2.120.362 people. East Kalimantan (14.7%) and Yogyakarta Special Region (14.6%) had the highest stroke prevalence in Indonesia.[2]

The pathophysiology of stroke begins with damage to blood vessel endothelial cells caused by a complex cascade that activates the systemic inflammatory response in both ischemic and hemorrhagic strokes.[3] This inflammatory response activates the immune system, such as macrophages and T cells, then forms a plaque that attracts other inflammatory mediators. Inflammatory mediators of pro-inflammatory cytokines, free radicals, and proteases can induce plaque rupture and thrombosis. Both ischemic and hemorrhagic brain damage can stimulate the movement and migration of immune cells, predominantly neutrophils and macrophages, into the brain and induce a systemic inflammatory response.[4]

C-reactive protein (CRP) is a marker to detect systemic inflammatory status, evaluate therapy, and predict the risk of future atherosclerotic diseases such as stroke and cardiovascular disease.[1,3] It is produced several hr after the onset of tissue injury until it peaks in 48-72 hr.[5] Increasing inflammatory markers such as CRP, IL-1, and IL-6 contribute to the pathogenesis of the ischemic brain and worsen the functional neurological outcome.[6]

Lactate dehydrogenase (LDH) is a cytoplasmic enzyme, the end product of glycolysis, found in many body cells and tissues, including muscle, liver, and brain. The presence of extracellular LDH in serum indicates a process of cell or tissue damage caused by inflammatory processes or pathological conditions.[7,8] It can be found in severe infection and sepsis, malignancy, acute myocardial infarction, hypoxic-ischemic encephalopathy, liver diseases such as hepatic cirrhosis, and hepatic metastases.[7,9] Increased serum LDH is a marker of the process of intravascular hemolysis, thus making LDH a prognostic for patients with stroke. Although LDH is a negative indicator of functional outcomes for various diseases, the relationship between LDH and stroke is still unclear.[9]

Other inflammatory markers, such as procalcitonin and fibrinogen, play a role in the pathogenesis of stroke. Procalcitonin can lead to an inflammatory process that causes endothelial damage, thrombin formation, and microvascular disturbances.[10,11] Conversely, fibrinogen causes endothelial cell damage through an inflammatory process resulting in unstable atherosclerotic plaque progression.[12]

Several scores can be used to assess functional status, cognition, and stroke severity. The degree of severity of stroke can be evaluated by using the NIHSS (National Institutes of Health stroke scale), SSGM (*Skala Stroke Gadjah Mada*), and MRS (modified ranking scale). In contrast, the functional outcomes of stroke patients are measured by BI (Barthel index) scores, ADL (activities of daily Living), and IADL (instrumental activities of daily living). Cognitive outcomes were assessed using MMSE (mini-mental state examination) and Moca-Ina (Indonesian version of Montreal cognitive assessment) scoring. Functional status is essential in determining patient management, as prognostic testing using inflammatory markers is a good option.[1,2,13] However, studies related to LDH, CRP, procalcitonin, and fibrinogen markers on stroke outcomes ae still limited. This study aimed to determine the prognostic relationship between LDH, CRP, procalcitonin, and fibrinogen and stroke patient outcomes.

MATERIALS AND METHODS

Subject

This was a retrospective cohort study involving patients with stroke at Dr. Sardjito General Hospital, Yogyakarta from October 2020 to August 2021 who met the inclusion and exclusion critrai. The inclusion criteria were 1) patients who had been diagnosed with stroke assessed from anamnesis, physical examination, and head CT scan examination, 2) had complete laboratory examination, including CRP, LDH, procalcitonin, and fibrinogen on admission. The exclusion criteria were patients with incomplete variable data.

Variables measurement

C-reactive protein, LDH, fibrinogen, and procalcitonin variables were processed at the Clinical Pathology Laboratory of Dr. Sardjito General Hospital and measured by blood samples from subjects at admission. Measurement of functional status at the end of hospitalization was assessed by BI, ADL, and IADL, while stroke severity was evaluated by NIHSS, SSGM, and MRS. Cognitive status measures were considered by MMSE and Moca-Ina score. The NIHSS had a value range of 0-34, with the higher the value indicating the more severe the degree of stroke. The BI had a value range of 0-100, and SSGM had a value range of 0-38, with low values indicating severe functional impairment. The ADL had a value range of 0-18, and the IADL had a value range of 0-14, with higher values indicating severe functional impairment. The MRS score ranged from 0-6, with higher indicating severe functional impairment. The MMSE and Moca-Ina each have a score range of 0-30, with lower scores indicating worse cognition. Another variable was GCS to measure the level of consciousness. This GCS consists of four scales: Compos Mentis is where a person is fully awake and responsive, somnolence is where a person is drowsy but still responds to the tactile or auditory stimulus, stupor is where a person is difficult to wake and only responds to a vigorous stimulus and coma is where a person does not respond in any stimulus.[14] Follow-up was carried out at the end of hospitalization to determine the duration of hospitalization and the subject's last condition. This study was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta (KE/FK/0288/EC).

Statistical analysis

Characteristics of the subject were presented in tabular form. Numerical variables will be analyzed for normality of the data using Shapiro-Wilk, with a $p < 0.05$ indicating that the data was not normally distributed. A multivariate test was performed with adjustments for age, sex, and BMI (body mass index) for each variable with logistic regression (categorical dependent variable) or linear regression (numerical dependent variable). Significant inflammatory variables will be analyzed by the receiver operating characteristic curve (ROC) to determine the cutoff, and then Cox-regression analysis was performed to determine the hazard ratio (HR) of these inflammatory marker variables. SPSS version 20 was used for statistical analysis.

RESULTS

A total of 292 subjects were included in this study, with males 55.5% and females 44.5%. Based on the type of stroke, there were 213 infarction cases (77.7%) and 56 cases of hemorrhage (22.3%). Subjects who died amounted to 83 patients (30.4%). Initial characteristic data of subjects are presented in TABLE 1.

High CRP levels were significantly and independently associated with worsened GCS scores, ADL, IADL,

NIHSS, BI, SSGM, MRS, and higher mortality in stroke patients ($p<0.05$) as presented in TABLE 2. High LDH levels were significantly and independently associated with worsened GCS admissions and higher mortality ($p<0.05$). Conversly, fibrinogen and procalcitonin levels were not associated with stroke functional outcomes or stroke patient mortality ($p>0.05$). Meanwhile, increased levels of procalcitonin correlated with increased levels of CRP ($p <0.007$) and increased levels of fibrinogen associated with increased levels of CRP and LDH ($p<0.05$).

TABLE 1. Characteristics of subjects

Variable	Proportion (%)	Mean ± SD
Age (yr)	-	60.71±13.31
Gender (%)		
Male	162 (55.5)	-
Female	130 (44.0)	-
BMI (kg/m^2)	-	24.11±3.99
GCS (%)		
Coma	27 (9.2)	-
Sopor	27 (9.2)	-
Somnolence	39 (13.4)	-
Compos mentis	199 (68.2)	-
Stroke type (%)		
Infact	227 (77.7)	-
Hemorrhage	65 (22.3)	-
CRP (mg/dL)	-	44.97±54.77
LDH (U/L)	-	331.73±528.41
Procalcitonin (ng/mL)	-	3.79±8.18
Fibrinogen (mg/dL)	-	451.95±157.39
LoS (d)	-	6.76±5.24
ADL	-	12.76±5.68
IADL	-	11.02±4.06
NIHSS	-	10.97±8.99
Barthel Index	-	39.81±30.28
SSGM	-	23.13±11.49
MMSE	-	22.51±6.39
Moca-Ina	-	18.64±7.54
MRS	-	3.71±1.42
Mortality (%)		
Deceased	83 (30.9)	-
Alive	186 (69.1)	-

Note. BMI: body mass index; GCS: Glasgow coma scale; CRP: C-reactive protein; LDH: lactate dehydrogenase; LoS: length of stay; ADL: activities of daily living; IADL: instrumental activities of daily living; NIHSS: National Institutes of Health stroke scale; SSGM: Gadjah Mada stroke scale; MMSE: mini-mental state examination; Mona-Ina: Indonesian version of Montreal cognitive assessment; MRS: modified ranking scale; SD: standard deviasion.

TABLE 2. Relationship between CRP, LDH, fibrinogen, and procalcitonin to various variables in all types of stroke

Variable	CRP	LDH	Procalcitonin	Fibrinogen
Age (yr)[a]				
r-adjusted	0.142	0.043	0.189	0.103
p	0.034	0.475	0.189	0.390
Gender[b]				
Male	43.31±53.45	314.91±182.33	4.15±9.10	486.08±174.87
Female	47.10±56.55	352.82±767.85	3.31±6.86	419.67±133.31
p	0.762	0.084	0.838	0.221
LoS (d)[a]				
r-adjusted	0.034	0.032	0.015	0.175
p	0.611	0.597	0.914	0.141
GCS[a]				
r-adjusted	-0.228	-0.130	0.036	0.002
p	<0.001	0.028	0.797	0.986
ADL[a]				
r-adjusted	0.281	0.119	-0.010	0.022
p	<0.001	0.047	0.941	0.856
IADL[a]				
r-adjusted	0.262	0.063	0.024	-0.048
p	<0.001	0.291	0.864	0.694
NIHSS[a]				
r-adjusted	0.264	0.117	0.631	-0.074
p	<0.001	0.05	0.631	0.544
BI[a]				
r-adjusted	-0.307	-0.071	-0.002	0.065
p	<0.01	0.238	0.991	0.593
SSGM[a]				
r-adjusted	-0.254	-0.039	-	-0.047
p	0.003	0.607	-	0.839
MMSE[a]				
r-adjusted	-0.253	-0.162	-	0.067
p	0.02	0.098	-	0.853
Moca-Ina[a]				
r-adjusted	-0.207	-0.129	-	0.319
p	0.062	0.198	-	0.402
MRS[a]				
r-adjusted	0.283	0.052	0.022	-0.105
p	<0.001	0.419	0.875	0.390
CRP (mg/dL)[a]				
r-adjusted	-	0.319	0.362	0.437
p	-	<0.001	0.007	<0.001

TABLE 2. Cont

Variable	CRP	LDH	Procalcitonin	Fibrinogen
LDH, U/L[a]				
r-adjusted	0.344	-	0.219	0.356
p	<0.001	-	0.115	0.003
Procalcitonin (ng/mL)[a]				
r-adjusted	0.353	0.219	-	-0.035
p	0.011	0.115	-	0.863
Fibrinogen (mg/dL)[a]				
r-adjusted	0.437	0.356	-0.035	-
p	0.001	0.003	0.863	-
Stroke type[b]				
Infarct	49.26±56.27	339.62±587.40	3.97±8.44	473.25±170.89
Hemorrhage	30.03±36.57	304.04±221.78	1.58±3.01	388.05±81.57
p	0.017	0.495	0.165	0.072
Mortality[b]				
Deceased	76.84±58.43	454.12±953.90	5.15±9.90	463.73±170.86
Alive	32.36±47.45	287.97±170.20	1.76±3.93	447.17±146.95
p	<0.001	<0.001	0.061	0.859

Information: [a]Analysis using linear regression adjusted for age, sex, and BMI; [b]Analysis using logistic regression adjusted for age, sex, and BMI; LoS: length of stay; ADL: activities of daily living; CRP: C-reactive protein; GCS: Glasgow coma scale; IADL: instrumental activities of daily living; LDH: lactate dehydrogenase; MMSE: mini-mental state examination; Mona-Ina: Montreal cognitive assessment Indonesian version; MRS: modified ranking scale; NIHSS: National Institutes of Health stroke scale; SSGM: Gadjah Mada stroke scale.

Sub-analysis based on the type of stroke in TABLE 3 showed that high CRP levels significantly correlated with lower GCS, BI, SSGM MMSE, Moca-Ina, and worsened NIHSS, ADL, IADL, MRS scores in stroke infarct patients ($p<0.05$). In cases of stroke infarction who deceased, CRP levels were higher (81.53 mg/dL) than the surviving group (35.03 mg/dL; $p<0.001$). For hemorrhagic stroke, only CRP levels were significantly and independently related to mortality ($p=0.029$). High LDH levels correlated with worse GCS, ADL, and NIHSS scores ($p<0.05$) and were associated with higher mortality in stroke infarction ($p<0.001$). In hemorrhagic stroke, there was no significant relationship between LDH levels and patient outcomes ($p> 0.05$). Fibrinogen and procalcitonin levels were not significantly related to functional outcome and mortality from infarct or hemorrhage stroke ($p> 0.05$).

TABLE 3. Relationship between CRP, LDH, fibrinogen, and procalcitonin to infarction stroke and hemorrhagic stroke

Variable	CRP		LDH		Fibrinogen		Procalcitonin	
	Infarct	Hemor-rhagic	Infarct	Hemorrhagic	Infarct	Hemorrhag-ic	Infarct	Hemorrhagic
LoS[a]								
r-adjusted	0.034	-0.150	0.097	-0.065	-0.049	0.632	0.202	0.505
p	0.611	0.240	0.151	0.614	0.731	0.368	0.144	0.033
GCS[a]								
r-adjusted	-0.265	-0.174	-0.153	-0.097	-0.07	0.833	-0.086	0.140
p	<0.001	0.170	0.023	0.448	0.627	0.167	0.537	0.581
Mortality[b]								
Deceased	81.53±57.28	58.64±61.04	485.69±1069.65	337.11±201.79	5.46±10.31	-	486.91±187.20	387.57±61.48
Alive	35.03±49.23	22.23±38.91	284.18±143.49	302.81±251.01	1.85±4.01	-	463.13±160.14	392.22±68.78
p	<0.001	0.029	<0.001	0.397	0.063	-	0.720	0.918
ADL[a]								
r-adjusted	0.350	0.087	0.136	0.089	0.034	-	0.087	-0.060
p	<0.001	0.506	0.045	0.500	0.814	-	0.531	0.826
IADL[a]								
r-adjusted	0.330	0.107	0.079	0.040	0.068	-	0.011	-0.196
p	<0.001	0.412	0.245	0.764	0.635	-	0.938	0.466
NIHSS[a]								
r-adjusted	0.318	0.098	0.142	0.023	-0.085	0.949	0.004	-0.190
p	<0.001	0.452	0.035	0.863	0.552	0.051	0.975	0.482
BI[a]								
r-adjusted	-0.307	-0.214	-0.073	-0.097	-0.042	0.895	0.018	0.009
p	<0.001	0.098	0.278	0.459	0.772	0.105	0.894	0.974
SSGM[a]								
r-adjusted	-0.255	0.216	-0.047	0.097	-	-	-0.083	0.048
p	0.003	0.164	0.589	0.543	-	-	0.788	0.910
MMSE[a]								
r-adjusted	-0.253	0.081	-0.164	-0.208	-	-	0.120	-
p	0.020	0.727	0.130	0.379	-	-	0.778	-
Moca-Ina[a]								
r-adjusted	-0.270	0.215	-0.138	0.182	-	-	0.301	-
p	0.062	0.392	0.212	0.484	-	-	0.468	-
MRS[a]								
r-adjusted	0.283	0.094	0.068	0.037	0.065	-	-0.004	-0.474
p	<0.001	0.511	0.349	0.795	0.655	-	0.977	0.064

[a]Analysis using linear regression adjusted for age, sex, and BMI; [b]Analysis using logistic regression adjusted for age, sex, and BMI. The - sign indicates that the analysis could not be carried out because the number of subjects in each group did not meet; ADL: activities of daily living; CRP: C-reactive protein; GCS: Glasgow coma scale; IADL: instrumental activities of daily living; LDH: lactate dehydrogenase; MMSE: mini-mental state examination; Mona-Ina: Montreal cognitive assessment Indonesian version; MRS: modified ranking scale; NIHSS: National Institutes of Health stroke scale; SSGM: Gadjah Mada stroke scale.

TABLE 4. Survival analysis CRP dan LDH towards stroke mortality

Variable	Cut off	p	Hazard ratio	95% CI
CRP	>24.5	<0.001	3.225	1.96-5.29
LDH	>300	0.026	1.651	1.06-2.56

CI: confidence interval; CRP: C-reactive protein; LDH: lactate dehydrogenase

Logistic regression analysis included the four inflammatory marker variables above, and the predictor formula was obtained (12 x CRP) + LDH where the total values were 600, 1000, and >2000, indicating a stroke mortality rate of 26.25%, 47.5%, and >75%. TABLE 4 showed analysis using Cox regression, where CRP levels >24.5 mg/dL could increase mortality 3.2 times (p <0.001), and LDH levels >300 U/L could increase mortality 1.6 times in stroke patients (p = 0.026).

DISCUSSION

This study showed that elevated CRP levels (> 24.5) and high LDH (> 300) were associated with increased stroke mortality, especially in stroke infarction. This CRP is a marker of both acute and chronic systemic inflammation, where inflammation plays an essential role in the pathogenesis of cerebrovascular disease through the mechanism of atherosclerosis formation and plaque instability, which results in easy plaque rupture. Several studies had shown that inflammation can affect atherosclerotic plaques' composition, morphology, and stability, the most common cause of stroke infarction.[15,16]

On the other hand, LDH is a marker whose levels will increase if tissue damage occurs. Increased LDH levels are markers of intravascular hemolysis, thus contributing to prognostic factors in stroke.[17] Although the underlying mechanism in the relationship between LDH and stroke outcome and mortality is still unclear, several theories can explain the above conditions. First, LDH is an inflammatory biomarker in which inflammation is related to endothelial cell dysfunction. Second, LDH is an enzyme in many organ systems, and its levels will increase if there is a disturbance in these organs.[8,18]

The mechanism between CRP and hemorrhagic stroke is still unclear. However, several studies showed that CRP levels are associated with the formation of lesions in the white matter, which indicates the involvement of the inflammatory process in the brain's small blood vessels. Bleeding may result from the rupture of small vessels from lipo hyalinosis secondary to hypertension or amyloid angiopathy. Liu *et al.*[15] reported that hs-CRP (high sensitivity CRP) levels were associated with micro brain hemorrhages in the lobar and deeper structures.[14] Other studies showed that there was a relationship between increased CRP levels and the development of stroke, as seen in increased mortality and the incidence of intracerebral hemorrhage after thrombolysis.[18]

In this study, high LDH levels did not significantly correlate with functional outcomes and hemorrhagic stroke mortality. In contrast, previous studies demonstrated that LDH levels had a positive relationship with mortality and poor functional outcome in ischemic stroke patients and in hemorrhagic stroke at three months and one-year

follow-ups.[17] Study with a longer follow-up duration is needed to show a significant relationship between LDH and functional outcome.

In this study, the relationship between fibrinogen and procalcitonin was insignificant to stroke patients' functional outcome and mortality (> 0.05). Another study reported no significant difference between fibrinogen and stroke function outcomes (p = 0.416), and there was no significant difference in fibrinogen levels between stroke patients and the control group.[12,19] This differed from the study by Di Napoli *et al.*,[20] which reported a significant association between high fibrinogen levels and poor stroke function outcomes. For procalcitonin, several studies had shown mixed results. The study by Deng *et al.*[11] reported that procalcitonin levels were associated with stroke functional outcomes, as seen from the NIHSS score (<0.001). In contrast, the study by Miyakis *et al.*,[21] showed no significant association between procalcitonin levels with mortality and stroke function outcomes based on stroke subtype. Further study to investigate the relationship between procalcitonin and fibrinogen on functional outcomes and stroke mortality is still needed.

The limitations of this study were the small number of subjects; we did not differentiate between first stroke or recurrent stroke, and the short follow-up duration. Further research is needed regarding this study. However, based on the researchers' knowledge to the present time, studies have yet to examine the relationship between CRP, LDH, fibrinogen, and procalcitonin on mortality and functional outcome of stroke as assessed by various rating scales comprehensively in Indonesia.

CONCLUSION

This study showed that CRP >24.5 mg/dL and LDH >300 U/L at admission could predict worsened functional outcomes and increased mortality in stroke patients. Mortality and functional outcome of infarction stroke are associated with high CRP and LDH levels at admission, whereas only CRP is associated with mortality and functional development of hemorrhagic stroke.

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