ORIGINAL ARTICLE

Combination of five clinical data as prognostic factors of mortality after ischemic stroke

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ABSTRACT

BACKGROUND

The mortality rate after ischemic stoke is influenced by various factors. Prognosis after ischemic stroke can be predicted using a scoring system to help the doctor to evaluate patient's condition, neurologic deficits, and possible prognosis as well as make appropriate management decisions. The objective of this study was to identify the factors which determine mortality rates in patients after ischemic stroke and to determine the prognosis of ischemic stroke patients using the predictive mortality score.

METHODS

This was a nested case control study using data from the stroke registry and medical records of patients at the Neurology Clinic of Bethesda Hospital Yogyakarta between 2011-2015. Data was analysed using simple and multiple logistic regression analysis. The scoring was analyzed using receiver-operating characteristic (ROC) curve and the cut-off point using area under the curve (AUC).

RESULTS

Multiple logistic regression analysis showed a significant association between mortality of ischemic stroke patients and age (OR: 4.539, 95% CI: 1.974-10.439, p<0.001), random blood glucose (OR: 2.692, 95% CI: 1.580-4.588, p<0.001), non-dyslipidemia (OR: 2.313, 95% CI: 1.395-3.833, p=0.001), complications (OR: 1.609, 95% CI: 1.019-2.540, p=0.041), risk of metabolic encephalopathy (OR: 2.499, 95% CI: 1.244-5.021, p=0.010) and use of ventilators (OR: 17.278, 95% CI: 2.015-148.195, p=0.009).

CONCLUSIONS

Age, high random blood glucose level, complications, metabolic encephalopathy risk and the use of ventilators are associated with mortality after ischemic stroke. The predictive mortality score can be used to assess the prognosis of patients with ischemic stroke.

Keywords: Ischemic stroke, causes of mortality, predictive mortality score

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INTRODUCTION

Ischemic stroke is an episode of neurologic dysfunction that is caused by focal infarction of the brain, spinal cord and retina.[1] Each year the number of stroke patients is increasing. The prevalence of stroke (with the criterion of having been diagnosed by health personnel) of 8.3 per 1000 in the Indonesian Basic Health Research survey for 2007 (*Riskesdas 2007)* increased to 12.1 per 1000 in 2013 (for stroke respondents aged 15 years and above).[2] From data at the stroke registry of Bethesda Hospital for 2014 it is known that each trimester the number of patients with stroke is increasing. Of 2460 stroke patients at Bethesda Hospital between 2011 and 2013, a total of 9.47% had died.[3]

There are many factors that influence the cause of death in patients with ischemic stroke. Age, stroke subtype, atrial fibrillation, history of previous strokes/transient ischemic attack, albumin, creatinine, von Willebrand factor and ß-thromboglobulin are the factors that can predict death in patients with ischemic stroke.[4] The study of Mogensen et al.[5] on cause-specific mortality after stroke found that hypertension, smoking and alcohol consumption were not associated with cause-specific death. Previous studies reported that antihypertensive treatment directly after acute ischemic stroke may increase the mortality rate.[6] Other studies state that hypertension is the factor that is most frequently found in stroke patients. The factors that influence the prognosis of stroke patients are age, mean corpuscular volume (MCV), folic acid, and erythrocyte sedimentation rate (ESR). Advanced age, high MCV and low folic acid concentration in stroke patients are associated with a poor prognosis.[7] Çomoðlu et al.[8] in their study state that ESR level of patients at admission do not reflect stroke severity and cannot be used as a useful predictor for evaluating the short term prognosis of patients with acute ischemic stroke. The predictive factors of mortality in stroke patients are still varied and subject to debate.

The prognosis of ischemic stroke can be predicted by scoring. The use of a scoring system can help doctors in evaluating the initial condition of the patients, giving a rapid and accurate evaluation about deficits in stroke, thus facilitating communication between doctors and saving time for triage and treatment of the patients.[9] The objective of this study was to identify the factors that influence mortality in patients with ischemic stroke and determine the prognosis of these patients using the predictive mortality score.

METHODS

Design of study

This independent nested case control study was conducted at Bethesda Hospital, Yogyakarta, from February until March 2016 using secondary data from the stroke registry and medical records at Bethesda Hospital, Yogyakarta, from 2011 up to and including 2015.

Study subjects

The study subjects were patients with ischemic stroke over 40 years of age who had been diagnosed by head CT scan from 2011 to 2015 at Bethesda Hospital, Yogyakarta, whose data in the stroke registry and the medical records were complete, and had not been discharged against medical advice. Sample size was calculated according to the formula for differences in proportions of two populations. Based on the formula for sample size calculation, the sample comprised 179 deceased patients and 179 live patients so that the total sample size required was 358 patients.

Measurements

The age of the patients was calculated from the number of years from birth up to the last data collection at the hospital. The level of consciousness was assessed with the Glasgow Coma Scale (GCS) or noted in the medical record as compos mentis or somnolence or stupor or

coma. Muscle strength was assessed on the Medical Research Council (MRC) scale. Systolic blood pressure, diastolic blood pressure, random blood glucose and leukocyte count were obtained from the results of examination at admission. Patients were declared to be at risk for metabolic encephalopathy due to intoxication, renal disorders (uremic encephalopathy), pulmonary or hepatic disorders (hepatic encephalopathy) from the changes in electrolyte or enzyme concentrations or ureum/creatinine concentrations (sodium concentration <125 mmol/L or SGOT or SGPT or ureum or creatinine concentration >3 times the normal concentrations). Patients were declared have a history of hypertensive disease if they had ever been diagnosed with hypertension or consumed antihypertensive medications, or had blood pressures of >140/90 mmHg at 2 readings. Patients were declared to have atrial fibrillation by a cardiologist on the basis of their EKG. Patients were declared to have a history of dyslipidemia if they had ever been diagnosed with dyslipidemia or consumed statins/fibrate, or their cholesterol concentration was >200 mg/dL or triglycerides >150 mg/dL (fasting) or HDL <40 mg/dL or LDL >100mg/dL. Patients were declared to have a history of diabetes mellitus if they had ever been diagnosed with diabetes mellitus or consumed antidiabetics, or from the results of laboratory examination of random blood glucose of ≥200 g/dL or fasting blood glucose of ≥126 g/dL. The complications that were investigated in this study were the other disorders that emerged during hospitalization of the stroke patients and were noted in the medical records, i.e. gastrointestinal bleeding, dysphagia and urinary tract infections.

Data analysis

Data were analyzed by descriptive analysis and statistical analysis. Descriptive analysis comprised characteristic data of all patients, whereas statistical analysis comprised univariate, bivariate and multivariate analysis and validation tests using receiver-operating characteristic (ROC) curves, whereas for cut-off point the area under the curve (AUC) was used. The discrimination model was determined from the area under the ROC curve that was calculated by nonparametric methods. The area under the ROC curve is a measure of total predictive discrimination to separate patients with good outcomes from patients with poor outcomes. A ROC curve area of 0.5 indicates no discrimination, and an area of 1.0 indicates perfect discrimination. Determination of the cut-off point in this study was evaluated by logistic regression to obtain the largest area under the curve.[10]

Ethical clearance

This study was observational on secondary data from the registry. For this study ethical clearance was obtained from the Research Ethics Committee, Faculty of Medicine, Duta Wacana Christian University, under no. 152/ C/16/ FK/ 2016.

RESULTS

Table 1 above shows the baseline characteristics of all study samples that were analyzed descriptively. A total of 358 patients meeting the inclusion and exclusion criteria were recruited into this study, consisting of 203 male patients (56.7%) and 155 female patients (43.3%). The most numorous subjects were in the age range of >70 years, comprising 121 patients (33.8%). The most frequent onset to admission time was >24 hours (44.1%).

The relationship of predictive factors of mortality with the dependent variables listed in Table 2 above shows that the variables that have a significant relationship with mortality in ischemic stroke patients ($p<0.05$) are age, level of consciousness, muscle strength, side of weakness, systolic blood pressure, diastolic blood pressure, leukocyte count, random blood glucose, history of dyslipidemia, complications, risk of metabolic encephalopathy and use of ventilators.

Table 1. Baseline characteristics of all patients

Characteristic	n=358	%	Died	%
Gender				
Male	203	56.7	104	29.1
Female	155	43.3	75	20.9
Age				
40-50 years	40	11.2	10	2.79
51-60 years	81	22.6	38	10.61
61-70 years	116	32.4	57	15.92
>70 years	121	33.8	74	20.67
Level of consciousness				
Compos mentis	198	55.3	78	21.79
Somnolence	107	29.9	63	17.59
Stupor	50	14.0	35	9.78
Coma	3	0.84	3	0.84
Onset to admission time				
< 3 hours	36	10.1	17	4.75
3-6 hours	72	20.1	35	9.78
6-12 hours	51	14.2	25	6.98
12-24 hours	41	11.5	18	5.03
>24 hours	158	44.1	84	23.46
Smoking				
Yes	14	3.91	4	1.12
No	344	96.1	175	48.88
Muscle strength				
Active movement against full resistance	66	18.4	25	6.98
Active movement against gravity and some resistance	53	14.8	18	5.03
Active movement against gravity	40	11.2	18	5.03
Active movement with elimination of gravity	29	8.1	17	4.75
Few visible contractions	99	27.7	55	15.36
No visible contractions	10	2.8	3	0.84
Undetermined	61	17	43	12.01
Side of weakness				
Neither	77	21.5	33	9.22
Right	119	33.2	59	16.48
Left	119	33.2	57	15.92
Right and left	15	4.2	8	2.23
Undetermined	28	7.8	22	6.15
Systolic BP (mmHg)				
≤129	64	17.9	41	11.45
130-139	48	13.4	21	5.87
≥140	246	68.7	117	32.68
Diastolic BP (mmHg)				
≤84	127	35.5	76	21.23
85-89	0	0	0	0
≥90	231	64.5	103	28.77
Leukocyte count ($x10^3/mm^3$)				
≤11	202	56.4	91	25.42
>11	156	43.6	88	24.58
Random blood glucose (g/dL)				
<200	266	74.3	120	33.52
≥200	92	25.7	59	16.48
Atrial fibrillation				
Yes	16	4.5	8	2.23
No	342	95.5	171	47.77
History of diabetes mellitus				
Yes	18	5	13	3.63
No	340	95	166	46.37

Table 1. Cont.

Characteristic	n=358	%	Died	%
History of hypertension				
Yes	189	52.8	90	25.14
No	169	47.2	89	24.86
History of dyslipidemia				
Yes	107	29.9	39	10.89
No	251	70.1	140	39.11
Complications				
Yes	190	53.1	107	29.89
No	168	46.9	72	20.11
Risk of metabolic encephalopathy				
Yes	50	14	36	10.06
No	308	86	143	39.94
History of heart failure				
Yes	5	1.4	2	0.56
No	353	98.6	177	49.44
Use of ventilators				
Yes	14	3.9	13	3.63
No	344	96.1	166	46.37

Table 2. Relationship between predictive factors of mortality and death of ischemic stroke patients

Variable	Died (179)	Live (179)	OR	95%CI	p
Gender					
Male	75	80	Ref		0.594
Female	104	99	0.89	0.58-1.35	
Age					
40-50 years	10	30	Ref		
51-60 years	38	43	2.65	1.07 - 6.70	
61-70 years	57	59	2.90	1.22 - 7.02	
>70 years	74	47	4.72	1.99 - 11.46	
Level of consciousness					
Compos mentis	78	120	Ref		
Somnolence	63	44	2.20	1.33 - 3.66	
Stupor	35	15	3.59	1.76 - 7.41	
Coma	3	0	6.13	0.63 - 146.63	
Onset to admission time					
<3 hours	17	19	Ref		
3-6 hours	35	37	1.06	0.44 - 2.54	
6-12 hours	25	26	1.07	0.42 - 2.76	
12-24 hours	18	23	0.87	0.32 - 2.37	
>24 hours	84	74	1.27	0.58 - 2.78	
Smoking					
No	175	169	Ref		0.102
Yes	4	10	0.38	0.11-1.25	
Muscle strength					
Active movement against full resistance	25	41	Ref		
Active movement against some resistance	18	35	0.84	0.37 - 1.92	
Active movement against gravity	18	22	1.34	0.56 - 3.22	
Active movement with elimination of gravity	17	12	2.32	0.87 - 6.24	
Few visible contractions	55	44	2.05	1.03 - 4.08	
No visible contractions	3	7	0.70	0.13 - 3.44	

Table 2. Cont.

Variable	Died (179)	Live (179)	OR	95%CI	p
Undetermined	43	18	3.92	1.75-8.84	
Side of weakness					
Neither	33	44	Ref		
Left	57	62	1.23	0.66-2.28	
Right	59	60	1.31	0.71-2.43	
Both	8	7	1.52	0.44-5.28	
Undetermined	22	6	4.89	1.63-15.29	
Systolic BP (mmHg)					
≤129	41	23	Ref		
130-139	21	27	0.44	0.19 - 1.00	
≥140	117	129	0.51	0.28 - 0.93	
Diastolic BP (mmHg)					
≤84	76	51	Ref		
85-89	0	0			
≥90	103	128	0.54	0.34-0.83	
Leukocyte count ($x10^3/mm^3$)					
≤11	91	111	Ref		0.033
>11	88	68	1.57	1.03-2.40	
Random blood glucose (g/dL)					
<200	120	146	Ref		0.002
≥200	59	33	2.17	1.33-3.55	
Atrial fibrillation					
No	171	171	Ref		1.000
Yes	8	8	1.00	0.36-2.72	
History of diabetes mellitus					
No	166	174	Ref		0.053
Yes	13	5	2.72	0.95-7.81	
History of hypertension					
No	89	80	Ref		0.341
Yes	90	99	0.81	0.53-1.23	
History of dyslipidemia					
No	140	111	Ref		0.001
Yes	39	68	0.45	0.28-0.72	
Complications					
No	72	96	Ref		0.011
Yes	107	83	1.71	1.13-2.61	
Risk of metabolic encephalopathy					
No	143	165	Ref		0.001
Yes	36	14	2.96	1.53-5.72	
History of heart failure					
No	177	176	Ref		0.625
Yes	2	3	0.66	0.10-4.01	
Use of ventilators					
No	166	178	Ref		0.001
Yes	13	1	13.94	1.80-107.73	

Table 3. Multivariate analysis with logistic regression of mortality risk factors

Variable	OR	95% CI	p
Age (>50 years)	4.539	1.974 – 10.439	<0.001
High random blood glucose	2.692	1.580 – 4.588	<0.001
Non-dyslipidemia	2.313	1.395 – 3.833	0.001
Complications	1.609	1.019 – 2.540	0.041
Risk of metabolic encephalopathy	2.499	1.244 – 5.021	0.010
Use of ventilators	17.278	2.015 – 148.195	0.009

The data in Table 3 on multivariate analysis with logistic regression list the variables that have a significant relationship with mortality in ischemic stroke patients, i.e. age, random blood glucose concentration, non-dyslipidemia, complications, risk of metabolic encephalopathy and use of ventilators ($p<0.05$).

The results of the analysis show that there are variables that are associated with mortality in ischemic stroke patients, i.e. age (OR: 4.539, 95% CI: 1.974-10.439, $p<0.001$), random blood glucose (OR: 2.692, 95% CI: 1.580-4.588, $p<0.001$), non-dyslipidemia (OR: 2.313, 95% CI: 1.395-3.833, $p<0.001$), complications (OR: 1.609, 95% CI: 1.019-2.540, $p=0.041$), risk of metabolic encephalopathy (OR: 2.499, 95% CI: 1.244-5.021, $p=0.010$) and use of ventilators (OR: 17.278, 95% CI: 2.015-148.195, $p=0.009$). The discrimination value of the scoring model in this study was 0.692; (95%CI 0.638-0.746; $p<0.001$). The larger the AUC the better the overall accuracy of the test. In this study the AUC value lies between 0.50 and 0.75, thus it can be said that the overall accuracy of the test is fair. The value of $p<0.001$ shows that the test is proven to be able to predict the mortality.

DISCUSSION

Based on the results of the study it is known that with advancing age, the mortality risk in stroke patients is also increased. Patients who are over 50 years old have a higher mortality risk as compared with patients who are less than 50 years old. According to the study by Fonarow et al.[11] elderly patients have a higher prevalence of disorders such as atrial fibrillation, hypertension, coronary heart disease, a history of stroke and a smoking habit. Elderly patients commonly die in hospital instead of at home, for each 10-year increase in age.

Patients with high random blood glucose have a 2.6 times higher mortality risk compared with patients with normal random blood glucose. From a study on focal experimental ischemia by Piironen et al.[12] it is known that hyperglycemia can increase the size of the infarct and decrease the therapeutic window of recanalization.

Patients without dyslipidemia have a 2.3 times higher mortality risk than do patients with dyslipidemia. That dyslipidemia is a factor that reduces the mortality risk in patients with ischemic stroke is still a controversial issue. According to Sohail et al.[13] high concentrations of triglycerides and low-density lipoprotein (LDL) and low concentration of high-density lipoprotein (HDL) are associated with high scores on the modified Rankin Scale (mRS), with severe stroke and poor clinical outcomes. The results of the aforementioned study contradict those of the study by Muhammad et al.[14] who showed that patients with high total cholesterol concentrations have good clinical outcomes, since the cholesterol functions as a buffer for neutralizing free radicals and preventing injury to neural tissues.

Patients with complications such as gastrointestinal bleeding, urinary tract infections, and dysphagia have a 1.6 times higher mortality risk compared with patients without complications. According to a study conducted by Ogata et al.[15] gastrointestinal bleeding after the onset of stroke can cause a decrease in hemoglobin concentration, neurological damage, poor functional results and death. Another complication, i.e. urinary tract infection occurring during hospitalization of the stroke patients, such as put forward by Poisson et al.[16] have a characteristic impact, i.e. increased duration of hospital stay, increased health care costs, exposure to intravenous antibiotics, the risk of bacteriemia, decreased neurological status, poor clinical outcomes, and increased mortality risk.

Patients with a risk of metabolic encephalopathy have a 2.4 times higher mortality risk compared with patients without a risk of metabolic encephalopathy. The study conducted by Rodrigues et al.[17] about 'Hyponatremia in the prognosis of acute ischemic stroke' showed that hyponatremia is associated with mortality in patients with acute ischemic stroke. According

to Zhang et al.[18] the serum urea concentration of patients with acute ischemic stroke who are treated with intravenous tissue plasminogen activator (r-tPA) is independently associated with poor clinical results and death of the patients.

Patients who use ventilators during hospitalization have a 17.2 times higher mortality risk compared with patients who do not use ventilators. The study by Mayer et al.[19] states that two-thirds of stroke patients who use mechanical ventilators die during hospitalization and the majority of patients who survive experience severe disabilities. Patients who experience coma or worsening of their clinical condition after intubation have an extremely low chance of survival.

The discrimination value of the scoring model in this study is 0.692 (95% CI 0.638-0.746; $p<0.001$). The larger the AUC the better the overall accuracy of the test. In this study the AUC value lies between 0.50 and 0.75, thus it may be said that the overall test accuracy is fair. This value shows that this model is proven to be able to predict mortality.

One study demonstrates the importance of staffing levels and having a reasonable catchment population/stroke service as key factors associated with a better mortality outcome in stroke, which is one of the biggest killers globally.[20] Variable staff composition in hospitals was not investigated in our study and is one of the limitations of the study.

Another limitation of the present study is the nested case control design using secondary data, i.e. from the stroke registry and medical records of ischemic stroke patients at Bethesda Hospital, Yogyakarta. A limitation that is difficult to avoid is that the investigators were unable to control the condition and quality of the measurements performed by other persons in the past, because of the use of secondary data.

It is hoped that clinicians may be able to perform a good evaluation of the condition of the patients and appropriately determine the prognosis of these patients so that the patients' condition can be reported more accurately to their families. If in the future similar studies will be conducted, it is suggested that they use a different study method, e.g. a prospective cohort study using primary data so that the patients may be directly followed up.

CONCLUSIONS

Age, high random blood glucose concentration, complications, risk of metabolic encephalopathy, and use of ventilators are associated with mortality in ischemic stroke patients. The management of ischemic stroke should focus on the prevention of complications, thus decreasing mortality risk.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest with the parties associated in this study.

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CONTRIBUTION

RTP, TB and EA contributed to prepare the manuscript. RTP contributed to design the research, and responsible for the final content RTP, TB and EA contributed to collected and analyzed the data; Rizaldy Pinzon contributed to wrote the manuscript, and all authors read and approved the final manuscript.

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