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ORIGINAL RESEARCH

Characteristic of Acute Ischemic Stroke Patients Based on TOAST Classification During COVID-19 Pandemic Era: A Single Centre Study

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Introduction: The categorization system used in the Trial Org 10172 classification in Acute Stroke Treatment (TOAST) provided more insight into the causal process. The aims of this study were to characterize individuals with acute ischemic stroke using the TOAST criteria and to determine risk variables for patients with acute ischemic stroke during the COVID-19 pandemic.

Methods: A cross-sectional study was done on the medical records of acute ischemic stroke patients at Hasan Sadikin Hospital (RSHS) Bandung, Indonesia, who were hospitalized in the Neurology Department of Hasan Sadikin Hospital from January to December 2021. Eligible patients were divided into 2 groups, with and without COVID-19 infection.

Results: There were 136 participants with acute ischemic stroke. Thirty-one percent of strokes were caused by atherosclerosis in the large arteries (LAA), followed by small-vessel occlusion (SVO) (25%), cardioembolism (CE) (22.1%), an undetermined cause (21.3%), and an other etiology (1.5%). CE risk factor was atrial fibrillation ($p < 0.001$), while hypertension, diabetes, and smoking were significant for LAA ($p < 0.05$). However, in patients with COVID-19 who had an acute ischemic stroke, most of the subtypes were stroke of undetermined etiology (76%), and hypercoagulation was the main risk factor ($p < 0.001$).

Conclusion: Patients with and without COVID-19 show varied distributions of stroke subtypes according to the TOAST categorization. Hypercoagulation is a major risk factor for stroke of undetermined etiology in individuals with COVID-19 who suffer from acute ischemic stroke. Increased viral-mediated endothelial inflammation leading to aberrant coagulopathy may explain the correlation between COVID-19 and acute ischemic stroke.

Keywords: acute ischemic stroke, TOAST, COVID-19, pandemic

Introduction

Stroke ranks high among the primary causes of mortality and disability globally.[1] In 2020, 1 in 6 deaths from cardiovascular disease were directly attributable to stroke.[2] Ischemic strokes, in which blood supply to the brain is interrupted, account for over 87% of all strokes.[3] Stroke is reported in 2–6% of hospitalized patients with COVID-19, and acute cerebrovascular disease is the most severe complication of COVID-19 due to abnormalities in cascade coagulation according to cohort studies. Treatment for Acute Stroke used the Trial Organization 10172 classification (TOAST) to further categorize strokes into those caused by Small Vessel Occlusion (SVO), cardioembolism (CE), Large-Artery Atherosclerosis (LAA), and stroke of undetermined etiology.[1] Patients diagnosed with SARS-CoV-2 (severe acute respiratory syndrome caused by coronavirus-2) have been proven to be at a higher risk of cerebrovascular events.[4–7] Patients with COVID-19 may have a hypercoagulable state and an increased rate of thromboembolic events. Symptoms involving the nervous system are on the increase and more recognition, despite the fact that respiratory issues are more commonly reported. A large series of patients hospitalized during the pandemic period revealed that 56% of those afflicted had a low but clinically significant risk of acute ischemic stroke (AIS), despite not fitting into the TOAST category.[8,9] The objectives of this study were to evaluate the features of acute ischemic stroke patients according to TOAST criteria and to identify risk factors for acute ischemic stroke patients during the COVID-19 pandemic period.

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Methods

This cross-sectional study was undertaken at Hasan Sadikin Hospital (RSHS), Bandung, West Java's tertiary care and primary referral hospital, using medical records of patients treated in the Neurology Department from January to December 2021. Patients who fulfilled the criteria established by the World Health Organization for the diagnosis of an acute ischemic stroke were included in this study. These patients had to have focal clinical symptoms or global cerebral dysfunction that lasted for more than 24 hours and had to have been caused solely by vascular factors. Subjects that were ruled out were those suffering strokes caused by hemorrhagic, long-term brain ischemia, transient ischemic attack (TIA), and having poor medical records data.

There were 136 patients whose data were considered eligible for inclusion (35 cases were excluded due to lack of medical records). Patients' demographic information, risk factors (such as hypertension, diabetes type 2, dyslipidemia, myocardial infarction, and atrial fibrillation), and examination outcomes (including stroke severity using National Institute of Health Stroke Scale (NIHSS), laboratory, and radiographic findings) were recorded. All subjects had radiographic, electrocardiographic, and cerebral computed tomography (CT) data collected, with the majority of patients additionally having echocardiography, Transcranial Doppler (TCD) and Carotid Doppler (CD) ultrasonography. Eligible patients were divided into 2 groups, with and without COVID-19 infection and patients whose COVID-19 status was determined to be positive based on nasopharyngeal or oropharyngeal Real Time Polymerase Chain Reaction (RT-PCR) swab results were included in this study. The presence of a hypercoagulable condition was determined by either an increase in the fibrinogen value (normal value 238–498 mg/dL) or an increase in the D-dimer value (normal value 0.55 mg/L).

The following are the five categories that are used to classify ischemic stroke according to TOAST criteria: (1) Clinical and radiographic evidence of more than 50% blockage or stenosis of an artery or a major branch of the brain's cortical arteries characterizes the condition known as LAA; (2) SVO, which is described as clinical lacunar syndrome (but not cortical dysfunction), whereas lesions on CT or Magnetic Resonance Imaging (MRI) should be smaller than 1.5 cm in diameter; (3) In the absence of evidence for other subtypes of stroke, CE is suspected when at least one significant cardiac risk factor for embolism is present; (4) Stroke of other determined etiology if additional risk factors for stroke are present (such as a hypercoagulable condition or a nonatherosclerotic vasculopathy) but no other characteristics of a specific subtype of stroke are present; (5) In the case where there is more than one possible cause of a stroke, but the inquiry does not uncover an etiology for the condition, a patient is said to have had a stroke of undetermined etiology.

This study complied with all relevant ethical regulations (including The Declaration of Helsinki) and covering patient data confidentiality. The correct ethics procedure were followed.

The study was conducted after obtaining ethical approval from the research ethics committee Hasan Sadikin General Hospital Bandung (LB.02.01/X.6.5/402/2022).

Result

Out of the total number of 136 patients, 81 (59.6%) were male and 55 (40.4% were female). Ages ranged from 20 to 88, with a mean (±SD) of 58.5 years. There were 38 patients (27.9%) were 65 or older (Supplementary Material). There were 61% patients having a moderate NIH Stroke Scale score. In terms of stroke subtypes, LAA was the most prevalent (30.1%), followed by SVO (25%), CE (22%), etiology of undetermined (21.3%), and other specified etiology (1.6%). The prevalence of hypertension was the highest among the risk factors, accounting for 80.1%. Other risk factors were dyslipidemia in 61%, type 2 diabetes mellitus in 25.7%, smoking 27.2%, hyperuricemia 5.1%, history of previous stroke 47.8%, myocardial infarction 2.9%, congestive heart failure 10.3% and atrial fibrillation 15.4%. Patients with a hypercoagulable state were found in 84% of the COVID-19-positive patients with acute ischemic stroke.

Table 1 provides a comprehensive overview of the participants' characteristics. Prevalence of risk factors varied between etiological classifications. Among the 40 patients with the LAA subtype, hypertension was shown to be the most frequent risk factor, occurring in 97% of cases (p=0.001). Furthermore, type 2 diabetes was determined to be a significant (p=0.008) risk factor, affecting 32 individuals (78%). CE (63%) had hypertension as a significant risk factor (p=0.009).

Table 1 Clinical Characteristic Research Subjects

Characteristic	n (%)	p-value
Gender		
Male	80 (58.8)	0.929
Female	56 (41.2)	
Age (years)		
20–29	3	
30–39	5	
40–49	21	
50–59	45	
60–64	24	
≥65	38	0.463
NIHSS admission		
Mild	20 (14.7)	
Moderate	83 (61.0)	
Moderate-severe	31(22.8)	
Severe	2 (1.5)	
Onset		
<4.5 hours	23 (16.9)	
≥4.5 hours	113 (83.1)	
TOAST classification		
Large-artery Atherosclerosis	41 (30.1)	
Small-vessel Occlusion	34 (25.0)	
Cardioembolism	30 (22.1)	
Stroke of other determined etiology	2 (1.5)	
Stroke of undetermined etiology	29 (21.3)	
Infarct location based on CT-Scan		
Cortical	86 (63.2)	
Subcortical supratentorial	42 (30.9)	
Infratentorial	8 (5.9)	
Risk factors, n (%)		
Hypertension	109 (80.1)	0.018*
Diabetes Mellitus	36 (26.5)	1.000
Dyslipidemia	83 (61)	0.099
Smoking	37 (27.2)	0.021*
Hyperuricemia	7 (5.1)	1.000
Atrial Fibrillation	21 (15.4)	0.022*
Myocardial Infarction	4 (2.9)	0.186
Congestive heart failure	14 (10.3)	0.117
Hypercoagulation	27 (19.9)	0.000*
Stroke history	65 (47.8)	0.715
COVID-19		
Yes	25 (18.4)	
No	111 (81.6)	

Note: *Statistically significant.

COVID-19 status was verified in 25 of 136 patients with acute ischemic stroke (18.4%). Significantly (p<0.001), 21 patients (84%) with a positive COVID-19 status for acute ischemic stroke were hypercoagulable. The mean (SD) values of fibrinogen, prothrombin time, and D-dimer in acute ischemic stroke patients with COVID-19 were 480 mg/dL, 13 seconds, and 9.24 mg/L, respectively. Table 2 lists the most common risks and the strongest correlations between them across all subtypes. Data on demographics and clinical characteristics of individuals with COVID-19 and ischemic stroke are presented in Table 3.

Table 2 Correlation Risk Factor Based on TOAST Classification

	Large-Artery Atherosclerosis (n=41)	*p*-value	Small-Vessel Occlusion (n=34)	*p*-value	Cardio Embolism (n=30)	p-value	Other Determined Etiology (n=2)	*p*-value	Undetermined Etiology (n=29)	*p*-value
Gender, n (%)										
Male	21 (51)	0.237	21 (61)	0.687	20 (66)	0.323	2 (100)	0.114	16 (55)	0.652
Female	20 (49)		13 (39)		10 (34)		0 (0)		13 (45)	
Age (years), n (%)										
≥65 years	7 (17)	0.064	10 (29)	0.825	10 (34)	0.456	0 (0)	0.852	11 (37)	0.176
<65 years	34 (83)		24 (71)		20 (66)		2 (100)		18 (63)	
NIHSS admission, n (%)										
Mild	2 (5)		15 (44)		1 (3)		0 (0)		2 (7)	
Moderate	32 (78)		16 (47)		16 (53)		1 (50)		18 (62)	
Moderate-Severe	7 (17)		2 (6)		13 (44)		0 (0)		9 (31)	
Severe	0 (0)		1 (3)		0		1 (50)		0 (0)	
Onset, n (%)										
<4,5 hours	7 (17)		3 (9)		11 (37)		1 (50)		1 (4)	
≥4,5 hours	34 (83)		31 (91)		19 (63)		1 (50)		28 (96)	
Infarct location based on CT-Scan, n (%)										
Cortical	33 (80)		0 (0)		30 (100)		1 (50)		22 (76)	
Subcortical supratentorial	4 (10)		32 (94)		0 (0)		0 (0)		6 (21)	
Infratentorial	4 (10)		2 (6)		0 (0)		1 (50)		1 (3)	
COVID-19, n (%)										
Yes	2 (5)		2 (6)		0 (0)		2 (100)		19 (65)	
No	39 (95)		32 (94)		30 (100)		0 (0)		10 (35)	
Risk factors, n (%)										
Hypertension	40 (97)	0.001*	31 (91)	0.063	19 (63)	0.009*	0 (0)	0.098	19 (65)	0.026*
Diabetes Mellitus	12 (29)	0.627	11 (32)	0.308	5 (17)	0.198	0 (0)	0.860	8 (27)	0.824
Dyslipidemia	32 (78)	0.008*	25 (73)	0.084	11 (37)	0.002*	0 (0)	0.707	15 (52)	0.247
Smoking	19 (46)	0.001*	13 (38)	0.095	2 (7)	0.004*	0 (0)	0.854	3 (10)	0.021*
Hyperuricemia	3 (7)	0.430	1 (3)	0.680	1 (3)	1.000	0 (0)	0.944	2 (3)	0.641
Atrial Fibrillation	0 (0)	0.001	0 (0)	0.004	14 (47)	0.000*	0 (0)	0.898	7 (24)	0.155
Myocardial infarction	0 (0)	0.315	0 (0)	0.572	1 (3)	1.000	0 (0)	0.958	3 (10)	0.030*
Congestive heart failure	0 (0)	0.011	0 (0)	0.021	11 (37)	1.000	0 (0)	0.919	3 (10)	1.000
Hypercoagulation	1 (2)	0.001*	0 (0)	0.001*	1 (3)	0.010*	2 (100)	0.546	23 (79)	0.000*
Stroke history	23 (56)	0.203	14 (41)	0.372	15 (50)	0.784	0 (0)	0.129	13 (45)	0.718

Note: *Statistically significant.

Table 3 Comparison of Clinical Characteristic Between Ischemic Stroke with and without COVID-19 Infection

Characteristic	With COVID-19 (n=25)	Without COVID-19 (n=111)	p-value
Gender, n (%)			
Male	16 (11.8)	64 (47.0)	0.56
Female	9 (6.6)	47 (34.6)	
Age (years)	60.80 ± 8.94	57.72 ± 12.18	0.163
≥65 years	9 (6.6)	29 (21.3)	
<65 years	16 (11.8)	82(60.3)	
NIHSS admission	13 (3–23)	10 (3–28)	0.118
Mild	2 (1.5)	18 (13.2)	
Moderate	14 (10.3)	69 (50.7)	
Moderate-Severe	8 (5.9)	23 (16.9)	
Severe	1 (0.7)	1 (0.7)	
TOAST classification, n (%)			
Large-artery Atherosclerosis	2 (1.5)	39 (28.7)	
Small-vessel Occlusion	2 (1.5)	32 (23.5)	
Cardioembolism	0 (0.0)	30 (22.0)	
Other determined etiology	2 (1.5)	0 (0.0)	
Undetermined etiology	19 (14.0)	10 (7.3)	
Infarction lesion based on CT-Scan, n (%)			
Cortical	16 (11.8)	70 (51.5)	
Subcortical supratentorial	7 (5.1)	35 (25.7)	
Infratentorial	2 (1.5)	6 (4.4)	
Risk factors n (%)			
Hypertension	15 (11.0)	94 (69.1)	0.010*
Diabetes Mellitus	5 (3.7)	31 (22.8)	0.417
Dyslipidemia	11 (8.1)	72 (53.0)	0.053
Smoking	2 (1.5)	35 (25.7)	0.017*
Hyperuricemia	1 (0.7)	6 (4.4)	1.000
Atrial Fibrillation	5 (3.7)	16 (11.8)	0.541
Myocardial infarction	2 (1.5)	2 (1.5)	0.154
Congestive heart failure	2 (1.5)	12 (8.8)	1.000
Stroke history	11 (8.1)	54 (39.7)	0.674
Hypercoagulation	21 (15.4)	6 (4.4)	0.000*

Note: *Statistically significant.

Discussion

According to our data, LAA was the most major cause of ischemic stroke. This study's findings are consistent with those reported by Harris et al, who evaluated ischemic stroke subtypes at Cipto Mangunkusumo Hospital in Jakarta and concluded that 59.6% of patients had LAA.[10,11]

This study involved a total of 136 individuals with ischemic stroke; however, the proportion of male patients to female patients was much higher. This is consistent with the findings of Harris et al, who discovered a greater percentage of male patients with acute ischemic stroke. Grau et al and Forster et al found that gender had a significant relationship with some subtypes of ischemic stroke, whereas Yu et al, Turin et al, and Al Hashel et al discovered that the association was not significant. We identified no significant relationship between gender and ischemic stroke subtype in this study.[11–15]

In this study, we identified 1.5% of patients with Stroke of Other Etiology, consistent with the findings of Harris et al, who detected 0.9% of patients with this subtype. Patients with acute ischemic stroke with COVID-19 and an elevation in coagulation markers were identified in this study as having Stroke of Other Etiology.[21] Twenty-nine patients (21.3%) were identified with cryptogenic stroke. This number is consistent with the incidence of cryptogenic stroke during the COVID-19 pandemic era of 19.7% (260/1319) patients found in a previous study by Ortega-Gutierrez et al, which gathered data on ischemic stroke patients independent of SARS-CoV-2 infection.[16]

Consistent with previous research by Marrone et al and Bahou et al,[17,18] hypertension was the most prevalent vascular risk factor. This study identified hypertension as the most prevalent vascular risk factor (80.1%), which was statistically significant in the LAA, SVO, and Undetermined Etiology subtypes. The formation and aggravation of intracerebral vasculopathy are two mechanisms by which chronic hypertension leads to stroke etiology. Increased microatheroma or lipohyalinosis in small arteries and atherosclerotic disease in medium to large arteries are additional mechanisms by which hypertension contributes to the course of stroke.[19] Dyslipidemia, which accounted for 61% of all cases, was the second most prevalent risk factor overall and was statistically significant in both the LAA and SVO subtypes. This proportion is more than the 46.05% seen in Shah et al's study of acute non-cardioembolic stroke patients with dyslipidemia.[20] The link between lipids and cerebrovascular illness is complicated. However, there is a clear correlation between cholesterol levels and ischemic stroke, and specifically atherosclerotic disease, with the highest link being between total cholesterol and Low Density Lipoprotein (LDL).[21]

The findings of this research are consistent with those of Harris et al, who found that atrial fibrillation was the primary risk factor for the cardioembolic subtype in 47% of cases ($p<0.001$). Atrial fibrillation is characterized by a failure of the atrium to contract, which leads to increased atrial pressure, tension, and dilatation of the atrium. These abnormalities provide the circumstances for the development of thrombi and blood clots. Atrial distention promotes atrial natriuretic peptide synthesis and reduces vasopressin secretion, which might result in hemoconcentration in atrial fibrillation. Atrial fibrillation is linked to poor hemostasis, endothelial dysfunction, and platelet activation, which elevates the likelihood of thrombus development.[10,24,25]

In patients with COVID-19, Stroke of Undetermined Etiology accounts for 76% of all acute ischemic stroke subtypes. Cryptogenic stroke was found to be much more common in the COVID-19-associated population by Ramos-Araque et al, at 42.6%, while a subtype of LAA was found to be as high as 32.4% by Shahjouei et al[22,23] Atherosclerosis, hypertension, and atrial fibrillation are all potential causes of stroke in COVID-19 individuals. However, in addition to the more traditional risk factors for stroke, COVID-19-associated processes may further raise the risk of stroke in affected individuals.[24]

In individuals diagnosed with COVID-19, hypercoagulation was the risk factor that was shown to have a statistically significant impact, followed by hypertension and dyslipidemia. The abnormalities in the coagulation cascade that can be triggered by SARS-CoV-2 can lead to an inflammatory response syndrome, greater production of proinflammatory mediators (cytokines and chemokines), initiation of thrombotic pathways, and hypercoagulable states, all of which contribute to cerebrovascular events.[25] The intrinsic anticoagulation pathway in COVID-19 patients is inhibited by a number of cytokines, including tumor necrosis factor-α, interleukin (IL)-6, and IL-1. Through this mechanism, coagulation may be activated and thrombin can be generated, leading to vascular blockage.[26] An exacerbated state of inflammation and coagulopathy, as well as an upsurge in viral replication, have all been linked to widespread organ failure.[27] We found three occurrences of concomitant cardio-cerebral infarction in patients reported having COVID-19.

Coagulopathy is closely linked to thrombotic events, and regardless of the severity, it has been frequently publicized in COVID-19 patients. D-dimer and fibrinogen levels are consistently elevated in more than 95% of individuals with severe COVID-19.[28,29] Stroke is reported in 2–6% of hospitalized patients with COVID-19, and acute cerebrovascular disease is the most severe complication of COVID-19 due to abnormalities in cascade coagulation according to cohort studies. SARS-CoV-2 can induce inflammatory response syndrome, higher production of pro-inflammatory mediators (cytokines and chemokines), activation of thrombotic pathways, and a hypercoagulation state due to abnormalities in cascade coagulation, which contributes to the cerebrovascular event. These responses may be because the viral invasion of the vascular endothelium (endotheliitis) contributes to vascular ischemia of the cerebral. Patients with COVID-19 may have a hypercoagulable state and an increased rate of thromboembolic events.[33] Standard tests for coagulation, such the prothrombin time (PT) and the activated partial thromboplastin time (aPTT), demonstrate no evidence of a procoagulant state and are either normal or just mildly prolonged. When compared to the more severe form of the disorder known as disseminated intravascular coagulation (DIC), this is far less common (DIC).[30] This research demonstrated a rise in D-dimer in stroke patients with COVID-19 [6.02 (0.29–33.85) mg/dL], which has a higher value than the study by Kim et al [0.95 (0.56–1.83) mg/dL], along with Ramos-Araque et al [0.78 (0.13–4.9)].[22,31] Fibrinogen was found to have a lower value (451± 151.7) than that obtained in the study by Bhatia et al (550 ±180).[32]

The lack of a control group was the primary limitation of this retrospective investigation. Hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking history, stroke history, and myocardial infarction history were the only risk variables included within the study. However, additional risk factors such as family history and Body Mass Index should also be taken into consideration (BMI). The ASPECT (Alberta Stroke Program Early CT Score) score data must therefore be compiled in order to quantify trends in ischaemic lesions. It is not possible to make a direct comparison between the group of stroke patients who do not have COVID-19 and the group of stroke patients who do have it in terms of their coagulation factors and also small amount of patients. In order to more precisely describe the prevalence of various subtypes of ischemic stroke and associated risk factors among patients hospitalized with acute ischemic stroke in Indonesia, a multicenter study may be necessary to attain a larger sample size.

Conclusion

During pandemic era, patients with acute ischemic stroke with COVID-19 had elevation in coagulation markers were identified in this study as having Stroke of Other Etiology. LAA was the most frequent cause of ischemic stroke in our study. LAA was shown to be linked to hypertension, dyslipidemia, and smoking, whereas the cardioembolic subtype was related to atrial fibrillation. However, hypercoagulation is a substantial risk factor for Stroke of Undetermined Etiology in this cohort. Increased viral-mediated endothelial inflammation may contribute to aberrant coagulopathy, which may explain why COVID-19 is related to acute ischemic stroke.

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Disclosure

There are no conflicting interests to consider.

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