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BRIEF COMMUNICATION

Age and Acute Ischemic Stroke Outcome in North American Patients With COVID-19

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BACKGROUND: Acute ischemic stroke (AIS) in the context of COVID-19 has received considerable attention for its propensity to affect patients of all ages. We aimed to evaluate the effect of age on functional outcome and mortality following an acute ischemic event.

METHODS AND RESULTS: A prospectively maintained database from comprehensive stroke centers in Canada and the United States was analyzed for patients with AIS from March 14 to September 30, 2020 who tested positive for SARS-CoV-2. The primary outcome was Modified Rankin Scale score at discharge, and the secondary outcome was mortality. Baseline characteristics, laboratory values, imaging, and thrombectomy workflow process times were assessed. Among all 126 patients with COVID-19 who were diagnosed with AIS, the median age was 63 years (range, 27–94). There were 35 (27.8%) patients with AIS in the aged ≤55 years group, 47 (37.3%) in the aged 56 to 70 group, and 44 (34.9%) in the aged >70 group. Intravenous tissue plasminogen activator and thrombectomy rates were comparable across these groups, (P=0.331 and 0.212, respectively). There was a significantly lower rate of mortality between each group favoring younger age (21.9% versus 45.0% versus 48.8%, P=0.047). After multivariable adjustment for possible confounders, a 1-year increase in age was significantly associated with fewer instances of a favorable outcome of Modified Rankin Scale 0 to 2 (odds ratio [OR], 0.95; 95 CI%, 0.90–0.99; P=0.048) and higher mortality (OR, 1.06; 95 CI%, 1.02–1.10; P=0.007).

CONCLUSIONS: AIS in the context of COVID-19 affects young patients at much greater rates than pre-pandemic controls. Nevertheless, instances of poor functional outcome and mortality are closely tied to increasing age.

Key Words: acute ischemic stroke ■ age outcomes ■ COVID-19 pandemic ■ SARS-CoV-2

The COVID-19 epidemic emerged in Wuhan, China in December 2019, and was associated with an unpreceded healthcare crisis.[1,2] The intersection of acute ischemic stroke and COVID-19–related disease represents a public health crisis that requires urgent communication to the medical community.[3,4] AIS in those without traditional risk factors is an emerging hallmark of COVID-19, unprecedented in the modern era of previous viral pandemics, and a distinguishing characteristic compared with other coronavirus infections. Of late, concerns have been raised about acute ischemic stroke

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Table 1. Characteristics of the Included Patients Stratified to Age Groups

	N*	≤55 (n=35)	56–70 (n=47)	>70 (n=44)	Total (n=126)	*P* Value
Sex	126					
Female		10 (28.6%)	25 (53.2%)	25 (56.8%)	60 (47.6%)	0.028
Male		25 (71.4%)	22 (46.8%)	19 (43.2%)	66 (52.4%)	
Race/ethnicity	125					
Black		13 (37.1%)	16 (34.0%)	16 (37.2%)	45 (36.0%)	0.251
White		9 (25.7%)	14 (29.8%)	19 (44.2%)	42 (33.6%)	
Others†		13 (37.1%)	17 (36.2%)	8 (18.6%)	38 (30.4%)	
Comorbidities						
Smoking	112	4 (11.8%)	9 (21.4%)	6 (16.7%)	19 (17.0%)	0.536
Atrial fibrillation	125	0 (0%)	4 (8.70%)	15 (34.1%)	19 (15.2%)	<0.001
Prior anticoagulation	118	1 (3.03%)	4 (9.09%)	10 (24.4%)	15 (12.7%)	0.015
Coronary artery disease	123	1 (2.86%)	6 (13.3%)	14 (32.6%)	21 (17.1%)	0.002
Congestive heart failure	117	1 (3.03%)	6 (13.6%)	9 (22.5%)	16 (13.7%)	0.055
Diabetes mellitus	122	10 (28.6%)	25 (54.3%)	17 (41.5%)	52 (42.6%)	0.066
Hypertension	126	17 (48.6%)	39 (83.0%)	39 (88.6%)	95 (75.4%)	<0.001
Hyperlipidemia	119	9 (26.5%)	29 (63.0%)	26 (66.7%)	64 (53.8%)	<0.001
Previous stroke	118	4 (11.8%)	14 (31.1%)	12 (30.8%)	30 (25.4%)	0.095
Peripheral vascular disease	106	0 (0%)	1 (2.44%)	3 (9.09%)	4 (3.77%)	0.134
Chronic kidney disease	114	9 (27.3%)	6 (14.6%)	14 (35.0%)	29 (25.4%)	0.105
Presentation						
Fever	102	22 (75.9%)	14 (36.8%)	7 (20.0%)	43 (42.2%)	<0.001
Cough	102	12 (41.4%)	16 (42.1%)	9 (25.7%)	37 (36.3%)	0.276
Dyspnea	102	9 (31.0%)	15 (39.5%)	16 (45.7%)	40 (39.2%)	0.488
Nausea or vomiting	102	1 (3.45%)	1 (2.63%)	1 (2.86%)	3 (2.94%)	0.98
Chills	102	4 (13.8%)	3 (7.89%)	1 (2.86%)	8 (7.84%)	0.269
Malaise or lethargy	102	3 (10.3%)	9 (23.7%)	3 (8.57%)	15 (14.7%)	0.14
Asymptomatic	104	5 (16.1%)	13 (34.2%)	12 (34.3%)	30 (28.8%)	0.176
Awareness of COVID-19 before stroke	100	12 (41.4%)	16 (41.0%)	10 (31.3%)	38 (38.0%)	0.634
Door to CT, min	81	22.0 [27.5]	22.0 [30.0]	23.5 [33.3]	23.0 [32.0]	0.889
Stroke site	81					
ICA		8 (34.8%)	6 (17.6%)	6 (25.0%)	20 (24.7%)	0.956
MCA		14 (60.9%)	22 (64.7%)	15 (62.5%)	51 (63.0%)	0.338
ACA		2 (8.70%)	2 (5.88%)	0 (0%)	4 (4.94%)	0.367
Vertebrobasilar		3 (13.0%)	7 (20.6%)	4 (16.7%)	14 (17.3%)	0.758

(*Continued*)

Table 1. Continued

	N*	≤55 (n=35)	56–70 (n=47)	>70 (n=44)	Total (n=126)	*P* Value
Admission NIHSS	106	15.0 [18.0]	11.0 [17.5]	12.0 [12.0]	12.0 [17.8]	0.174
ASPECTS	75	7.00 [3.50]	8.00 [4.00]	8.00 [2.00]	8.00 [3.00]	0.354
0–5		6 (30.0%)	9 (31.0%)	2 (7.69%)	17 (22.7%)	0.078
6–10		14 (70.0%)	20 (69.0%)	24 (92.3%)	58 (77.3%)	
Large vessel occlusion	118	16 (47.1%)	20 (46.5%)	18 (43.9%)	54 (45.8%)	0.956
Laboratories						
NLR	94	4.15 [10.5]	6.33 [9.91]	5.18 [8.26]	5.61 [10.4]	0.429
D dimer, ng/mL	87	420 [4830]	980 [4770]	944 [3240]	712 [4830]	0.918
INR	115	1.10 [0.20]	1.10 [0.30]	1.19 [0.20]	1.10 [0.28]	0.159
aPTT, s	107	31.5 [6.85]	30.6 [5.63]	29.9 [6.08]	30.6 [6.35]	0.468
C-reactive protein, mg/dL	97	21.8 [148]	34.1 [80.6]	24.0 [124]	33.7 [120]	0.742
Ferritin, ng/mL	95	816 [1230]	497 [639]	429 [472]	508 [695]	0.194
White blood cells, 1000/μL	122	8.30 [4.47]	8.67 [4.47]	7.90 [4.01]	8.25 [4.37]	0.483
Absolute neutrophil, 1000/μL	107	6.30 [4.70]	6.95 [4.70]	5.67 [3.01]	6.30 [4.42]	0.529
Absolute lymphocyte, 1000/μL	107	1.30 [1.00]	1.10 [0.475]	1.20 [0.540]	1.12 [0.670]	0.147
Platelets	122	266 [95.5]	247 [118]	215 [155]	243 [124]	0.269
Creatinine, mg/dL	123	1.04 [1.09]	1.10 [0.62]	1.10 [0.99]	1.10 [0.97]	0.529
GFR	117	60.0 [23.8]	60.0 [28.0]	55.5 [31.8]	60.0 [29.0]	0.092
LDH, U/L	82	490 [680]	339 [410]	450 [389]	415 [495]	0.342
Triglycerides, mg/dL	87	152 [57.3]	149 [116]	115 [66.0]	132 [81.5]	0.031
Troponin, ng/mL	93	0.02 [0.03]	0.03 [0.78]	0.04 [0.48]	0.03 [0.22]	0.074
CPK, U/L	71	201 [213]	115 [180]	104 [185]	127 [229]	0.163
LDL, mg/dL	82	101 [50.5]	84.0 [57.0]	58.0 [41.0]	80.5 [65.3]	0.081
HbA1c (%)	86	6.25 [3.45]	6.70 [2.85]	6.10 [1.20]	6.30 [2.18]	0.133
Aspirin	103	19 (65.5%)	32 (80.0%)	27 (79.4%)	78 (75.7%)	0.318
Plavix	87	4 (14.8%)	15 (44.1%)	9 (34.6%)	28 (32.2%)	0.049
Heparin	83	9 (36.0%)	11 (33.3%)	10 (40.0%)	30 (36.1%)	0.872
Low-dose enoxaparin	84	15 (53.6%)	13 (43.3%)	13 (50.0%)	41 (48.8%)	0.73
High-dose enoxaparin	76	4 (16.7%)	1 (3.45%)	0 (0%)	5 (6.58%)	0.048
IV tPA	123	11 (32.4%)	10 (22.2%)	8 (18.2%)	29 (23.6%)	0.331
Thrombectomy	118	11 (33.3%)	7 (16.3%)	10 (23.8%)	28 (23.7%)	0.212

ACA, Anterior Cerebral Artery; aPTT indicates activated partial thromboplastin time; ASPECTS, The Alberta Stroke Program Early CT Score; CPK, creatine phosphokinase; CT, computed tomography; ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; HbA1c, hemoglobin A1c; ICA, internal carotid artery; INR, international normalized ratio; IV tPA, intravenous tissue plasminogen activator; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; and NLR, neutrophil-lymphocyte ratio.

*Number of available data.

†Others includes Asian, Hispanic, Middle Eastern.

(AIS) secondary to large vessel occlusions in young patients with COVID-19.[5,6] We sought to analyze the clinical outcomes of AIS in patients positive with COVID-19 based on age.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. We studied all 126 patients with AIS who tested positive for SARS-CoV-2 and were admitted to 19 stroke centers in the United States and Canada, from March 14 to September 30, 2020. We stratified age into 3 prespecified groups (≤55, 56–70, and >70 years). Continuous variables were presented as median (interquartile range) and compared by Kruskal–Wallis test. Categorical variables were compared by the Pearson Chi-Square test. The impact of age on clinical outcomes of Modified Rankin Scale and mortality was investigated using univariable and multivariable logistic regression analyses. Covariates found to be significant upon univariable analysis (P≤0.05) were included with age (once as a continuous variable and again as a categorical variable) in the multivariable models. All analyses were performed using R software version 4.0.2. Institutional review board approval was obtained at all institutions, with consent waived per usual retrospective protocol.

RESULTS

The median age of the included patients was 63 years (range, 27–94). There were 35 (27.8%) patients with AIS in the aged ≤55 years group, 47 (37.3%) in the 56 to 70 group, and 44 (34.9%) in the >70 group. Almost one third (38%) of the sample were aware of COVID-19 diagnosis before stroke admission. We found significant differences between the 3 age groups on sex, atrial fibrillation, prior anticoagulation, coronary artery disease, hypertension, and hyperlipidemia (Table 1). The middle cerebral artery was the most commonly occluded vessel (63.0%) followed by the internal carotid artery (24.7%), vertebrobasilar segment (17.3%), and anterior cerebral artery (4.94%). National Institutes of Health Stroke Scale score was not significantly different between the 3 groups (median, 15.0 versus 11.0 versus 12.00; P=0.174). There was no difference in large vessel occlusion rates among the groups (47.1% versus 46.5% versus 43.9%, P=0.956). All hematologic and laboratory parameters were similar between the age groups except for triglycerides which were greater in the aged ≤55 years group who suffered strokes (median mg/dL, 152 versus 149 versus 115; P=0.031). Intravenous tissue plasminogen activator was given to 32.4%, 22.2%, and 18.2% of the age groups ≤55, 56 to 70, and >70 years, respectively (P=0.331). Similarly, there was no difference in thrombectomy rates between the age groups (33.3% versus 16.3%

Table 2. Outcomes of the Included Patients Stratified to Age Groups

	N*	≤55 (n=35)	56–70 (n=47)	>70 (n=44)	Total (n=126)	*P* Value
Post procedure mTICI	28					
0		1 (9.1%)	0 (0%)	0 (0%)	1 (3.6%)	
2		0 (0%)	1 (14.3%)	0 (0%)	1 (3.6%)	
2a		2 (18.2%)	2 (28.6%)	1 (10.0%)	5 (17.9%)	
2b		7 (63.6%)	0 (0%)	2 (20.0%)	9 (32.1%)	
3		1 (9.1%)	4 (57.1%)	7 (70.0%)	12 (42.9%)	
Discharge mRS	110					
0		4 (13.3%)	3 (7.69%)	1 (2.44%)	8 (7.27%)	0.222
1		5 (16.7%)	2 (5.13%)	2 (4.88%)	9 (8.18%)	
2		1 (3.33%)	3 (7.69%)	3 (7.32%)	7 (6.36%)	
3		8 (26.7%)	3 (7.69%)	6 (14.6%)	17 (15.5%)	
4		4 (13.3%)	6 (15.4%)	6 (14.6%)	16 (14.5%)	
5		1 (3.33%)	4 (10.3%)	3 (7.32%)	8 (7.27%)	
6		7 (23.3%)	18 (46.2%)	20 (48.8%)	45 (40.9%)	
Discharge mRS	110					
0–2		10 (33.3%)	8 (20.5%)	6 (14.6%)	24 (21.8%)	0.118
3–6		20 (66.7%)	31 (79.5%)	35 (85.4%)	86 (78.2%)	
sICH	116	4 (12.1%)	4 (9.30%)	1 (2.50%)	9 (7.76%)	0.277
Mortality	113	7 (21.9%)	18 (45.0%)	20 (48.8%)	45 (39.8%)	0.047

mRS indicates Modified Rankin Scale; mTICI, modified treatment in cerebral infarction; and sICH, symptomatic intracranial haemorrhage.
*Number of available data.

versus 23.8%, *P*=0.212). Rates of favorable outcomes (Modified Rankin Scale ≤2) at discharge were not significantly different between the groups (33.3% versus 20.5% versus 14.6%, *P*=0.118). There was a significantly lower rate of mortality between each age group favoring younger age (21.9% versus 45.0% versus 48.8%, *P*=0.047).

After adjusting for hypertension and National Institutes of Health Stroke Scale in the multivariable model (Tables 2 and 3), a 1-year increase in age was significantly associated with fewer instances of favorable outcome (odds ratio [OR], 0.95; 95% CI, 0.90–0.99; *P*=0.048). Furthermore, on mortality modeling and after adjusting for diabetes mellitus and National Institutes of Health Stroke Scale (Table S1), we observed significantly higher rates of mortality with each 1-year increase in age (OR, 1.06; 95% CI, 1.02–1.10; *P*=0.007).

DISCUSSION

AIS is known historically to be a disease of older patients, and our results suggest that patients still fare poorly as age increases in the context of COVID-19. Recently, it has been shown that patients with AIS infected with COVID-19 were more likely to be younger and have higher rates of large vessel occlusions compared with historical controls.[7] Similarly, in this study, there were 35 patients (27.8%) aged <56 years. As a virus which targets angiotensin-converting enzyme 2 receptors, it's suggested that direct endothelial damage may be at least partly to blame for the unprecedented burden upon the young and those without traditional risk factors.[8] AIS is known historically to be a disease of older patients, and our results suggest that patients still fare poorly as age increases in the context of COVID-19.

It is still uncertain what the exact mechanisms are that predispose this population to AIS, however, we corroborate early observations of better outcomes and lower rates of mortality in younger patients.[9] There are 2 major age-related discoveries that differentiate these findings from pre-COVID era AIS. The first is that the proportion of young patients experiencing AIS and particularly large vessel occlusions is vastly more than that before the pandemic. This is a crucial finding, and likely relates to hypercoagulability in the absence of traditional risk factors. Not only does this imply different pathophysiology in these patients, but seemingly also from other coronavirus pandemics.

The other surprising difference is that the risk of poor outcomes increases with every year of age. We believe this is crucial information to disseminate as although attention to the young is important, there is potential to ignore the fact that older patients fare worse to a degree at this also not precedented before the pandemic. In this case, there is reason to believe that there is an interaction between COVID-associated stroke, respiratory disease, and age. These associations with age merit further study.

This is a large study that was conducted through several centers in North America. Despite that, this study has some limitations. Principally, some variables that might affect the outcomes including socioeconomic status, local healthcare infrastructure, resources, and personal social support networks may also be at play. Furthermore, this study was done in healthcare centers and thus these patients have more

Table 3. Multivariable Binary Logistic Regression Models to Test for the Impact of Age on the Outcomes in Patients With Acute Ischemic Stroke Infected With COVID-19

Outcome		Variables	Multivariable Logistic Regression OR (95 CI%, *P* Value)
mRS 0–2	Model 1	Age (1 y increase)	0.95 (0.90–0.99, *P*=0.048)
		Hypertension	0.23 (0.04–1.19, *P*=0.092)
		Admission NIHSS score	0.74 (0.61–0.84, *P*<0.001)
	Model 2	Age, y (56–70 vs ≤55)	0.35 (0.05–2.06, *P*=0.257)
		Age, y (>70 vs ≤55)	0.20 (0.03–1.20, *P*=0.090)
		Hypertension	0.23 (0.04–1.16, *P*=0.086)
		Admission NIHSS score	0.76 (0.64–0.85, *P*<0.001)
Mortality	Model 1	Age (1 y increase)	1.06 (1.02–1.10, *P*=0.007)
		Diabetes mellitus	4.38 (1.65–12.29, *P*=0.004)
		Admission NIHSS score	1.09 (1.04–1.16, *P*=0.001)
	Model 2	Age, y (56–70 vs ≤55)	2.26 (0.65–8.44, *P*=0.208)
		Age, y (>70 vs ≤55)	4.76 (1.28–20.15, *P*=0.025)
		Diabetes mellitus	4.14 (1.58–11.42, *P*=0.005)
		Admission NIHSS score	1.09 (1.03–1.15, *P*=0.002)

All variables that had a *P*≤0.05 in the univariate model in Table S1 were included with age in the multivariable model. mRS indicates Modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

severe COVID-19 infections, which limits the generalizability to the whole population.

CONCLUSIONS

In North America, acute ischemic stroke in the context of COVID-19 is observed to affect young patients at much greater rates than pre-pandemic control periods. Importantly however, instances of poor functional outcome and mortality are closely tied to increasing age. Interactions between age, respiratory disease, and AIS may be important in COVID-19.

ARTICLE INFORMATION

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Author contributions: Dmytriw, Tiwari were responsible for statistical analysis, manuscript drafting, and critical revision. The remaining authors were responsible for data curation and critical manuscript revision.

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None.

Supplementary Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Univariable binary logistic regression analysis showing associations with Modified Rankin Scale (mRS) 0-2 and mortality.

	Univariate analysis -- mRS 0-2	Univariate analysis -- mortality
Variables	**OR (95 CI%, P-value)**	
Age (one year increase)	0.97 (0.93-0.99, p=0.036)	1.03 (1.01-1.06, p=0.028)
Age (56 - 70 vs ≤ 55)	0.43 (0.13-1.30, p=0.139)	2.92 (1.06-8.74, p=0.044)
Age (> 70 vs ≤ 55)	0.33 (0.10-1.01, p=0.057)	3.40 (1.25-10.13, p=0.021)
Sex (Male vs female)	1.07 (0.42-2.71, p=0.893)	1.41 (0.66-3.02, p=0.377)
Race (Caucasian vs Black)	1.48 (0.50-4.55, p=0.483)	0.45 (0.17-1.12, p=0.091)
Race (Others vs Black)	0.92 (0.25-3.25, p=0.901)	1.30 (0.51-3.37, p=0.580)
Smoking	0.81 (0.17-2.85, p=0.758)	2.17 (0.75-6.37, p=0.149)
Atrial fibrillation	2.37 (0.73-7.20, p=0.132)	1.07 (0.36-3.03, p=0.902)
Prior anticoagulation	1.41 (0.36-4.70, p=0.589)	1.32 (0.43-4.00, p=0.615)
Coronary artery disease	1.52 (0.44-4.62, p=0.479)	0.52 (0.16-1.50, p=0.247)
Congestive heart failure	1.73 (0.43-5.99, p=0.405)	0.87 (0.25-2.80, p=0.812)
Diabetes mellitus	0.40 (0.13-1.06, p=0.078)	3.71 (1.69-8.41, p=0.001)
Hypertension	0.35 (0.13-0.94, p=0.034)	1.36 (0.57-3.37, p=0.496)
Hyperlipidemia	0.90 (0.35-2.34, p=0.835)	1.09 (0.50-2.39, p=0.829)
Previous stroke	2.42 (0.88-6.58, p=0.082)	1.67 (0.69-4.04, p=0.257)
Chronic kidney disease	1.37 (0.44-3.91, p=0.570)	0.60 (0.21-1.54, p=0.300)
Admission NIHSS score	0.78 (0.68-0.87, p<0.001)	1.08 (1.03-1.13, p=0.001)
ASPECTS (6-10 vs 5-0)	3.55 (0.61-67.62, p=0.245)	0.34 (0.10-1.05, p=0.063)
IV tPA	1.19 (0.41-3.21, p=0.733)	0.62 (0.24-1.50, p=0.302)
High dose enoxaparin	2.56 (0.29-22.88, p=0.367)	0.51 (0.03-3.75, p=0.561)
Thrombectomy	0.38 (0.08-1.25, p=0.145)	1.08 (0.42-2.66, p=0.873)

NIHSS: National Institutes of Health Stroke Scale; ASPECTS: The Alberta Stroke Program Early CT Score; IV tPA: Intravenous tissue plasminogen activator