

Acute ischaemic stroke associated with SARS-CoV-2 infection in North America

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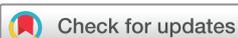
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ABSTRACT

Background To analyse the clinical characteristics of COVID-19 with acute ischaemic stroke (AIS) and identify factors predicting functional outcome.

Methods Multicentre retrospective cohort study of COVID-19 patients with AIS who presented to 30 stroke centres in the USA and Canada between 14 March and 30 August 2020. The primary endpoint was poor functional outcome, defined as a modified Rankin Scale (mRS) of 5 or 6 at discharge. Secondary endpoints include favourable outcome (mRS ≤2) and mortality at discharge, ordinal mRS (shift analysis), symptomatic intracranial haemorrhage (sICH) and occurrence of in-hospital complications.

Results A total of 216 COVID-19 patients with AIS were included. 68.1% (147/216) were older than 60 years, while 31.9% (69/216) were younger. Median [IQR] National Institutes of Health Stroke Scale (NIHSS) at presentation was 12.5 (15.8), and 44.2% (87/197) presented with large vessel occlusion (LVO). Approximately 51.3% (98/191) of the patients had poor outcomes with an observed mortality rate of 39.1% (81/207). Age >60 years (aOR: 5.11, 95% CI 2.08 to 12.56, p<0.001), diabetes mellitus (aOR: 2.66, 95% CI 1.16 to 6.09, p=0.021), higher NIHSS at admission (aOR: 1.08, 95% CI 1.02 to 1.14, p=0.006), LVO (aOR: 2.45, 95% CI 1.04 to 5.78, p=0.042), and higher NLR

level (aOR: 1.06, 95% CI 1.01 to 1.11, p=0.028) were significantly associated with poor functional outcome.

Conclusion There is relationship between COVID-19-associated AIS and severe disability or death. We identified several factors which predict worse outcomes, and these outcomes were more frequent compared to global averages. We found that elevated neutrophil-to-lymphocyte ratio, rather than D-Dimer, predicted both morbidity and mortality.

INTRODUCTION

Initially considered a respiratory illness, our understanding of COVID-19 has rapidly evolved. This past year, the global research community has undertaken an unprecedented and concerted effort to study the nature, consequences and therapeutic options for patients infected with this virus. It has become apparent that COVID-19 affects virtually every organ system, with a wide range of symptoms and severity.

One-third of patients with COVID-19 can have neurological manifestations with a higher frequency seen in those with more severe infection.¹ Studies evaluating these manifestations in greater detail have demonstrated a variety of presentations and complications.² Acute ischaemic stroke (AIS) has

been reported as both a presenting feature and complication of COVID-19, with variable estimates of incidence.^{1 3 4} The prognosis of patients with neurological COVID-19 manifestations may be influenced by demographic, geographic and socioeconomic factors as well as comorbidities.^{5 6}

We formed a multicentre consortium consisting of several North American centres to retrospectively analyse COVID-19 admissions with associated AIS. Our primary objective was to identify factors that are associated with poor outcome and mortality in these patients.

METHODS

Study design and inclusion criteria

The data that support the findings of this study are available from the corresponding author based on reasonable request. The number of participating comprehensive stroke centres totalled 30. The North American Neurovascular COVID-19 (NAN-C) Consortium is an investigator-initiated, retrospective cohort study of COVID-19 patients with AIS who presented to 19 medical centres in the USA and Canada, from 14 March to 30 August 2020. Patients were also included from an additional 11 centres in the USA and Canada that were recruited by the Society of Vascular and Interventional Neurology.

The inclusion criteria were patients who presented to any of the included centres for an AIS (with or without large vessel occlusion (LVO)) and tested positive for SARS-CoV-2 on qualitative reverse transcriptase PCR assays of nasal oropharyngeal swab samples.

Data collection

The following clinical baseline information was collected: age, sex, race, comorbidities, presence and type of COVID-19 related symptoms (fever, cough, dyspnoea, nausea or vomiting, chest pain and sore throat), baseline National Institutes of Health Stroke Scale (NIHSS) score, presence or absence of LVO on non-invasive baseline imaging, laboratory findings on admission and aetiology of the ischaemic stroke. Comorbidities included were smoking, atrial fibrillation, prior anticoagulation, coronary artery disease, congestive heart failure, diabetes mellitus, hypertension, hyperlipidaemia, previous stroke, peripheral vascular disease and chronic kidney disease. LVO was defined as an occlusion in one or more of the following: intracranial internal carotid artery, basilar artery, M1 and M2 segments of middle cerebral artery and P1 and P2 segment of the posterior cerebral artery. Aetiology of the ischaemic stroke was defined using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria divided into the following: cardioembolic, large-artery atherosclerosis, small-vessel occlusion, stroke of other determined aetiology and stroke of undetermined aetiology. Stroke of undetermined aetiology or cryptogenic stroke (CS) was further qualified as Embolic Stroke of Undetermined Source (ESUS) as defined by the 'Cryptogenic Stroke/ESUS International Working Group'.⁷ We chose to classify the severity of COVID-19 inflammation using systemic markers. We adopted the neutrophil-to-lymphocyte ratio (NLR) criteria used by Li *et al*⁸: NLR ≥ 4.5 was classified as severe and NLR ≥ 6.5 as very severe inflammation. D-dimer was used to assess hypercoagulability with a threshold value of ≥ 1000 ng/mL for hypercoagulability and ≥ 2000 ng/mL for severe hypercoagulability. Data on medication with anticoagulants/antiplatelet agents (aspirin, clopidogrel, heparin and enoxaparin) and treatment (intravenous tissue-type plasminogen activator (IV tPA) and mechanical thrombectomy) were also collected. The primary endpoint of this study was poor outcome, defined as a modified Rankin Scale (mRS) of 5 or 6 at discharge. Secondary endpoints were: (A) mortality at

discharge, (B) favourable outcome, defined as mRS score of ≤ 2 at discharge, (C) ordinal mRS (shift analysis), (D) symptomatic intracranial haemorrhage (sICH) and (E) occurrence of in-hospital complications that involved pulmonary, cardiac or renal systems and presence of deep vein thrombosis. Symptomatic intracranial haemorrhage was defined using the European Cooperative Acute Stroke Study III (ECASS III) criteria.⁹

Comparative analysis

For the comparative analysis, three historical control populations were chosen. These populations were specifically selected to minimise classification bias and compare study cohorts with the least possible overlap. For our non-COVID comparison we included the non-COVID all-cause ischaemic stroke cohort from the recently published 'GWTG-Stroke Acute Ischemic Stroke & COVID-19 Registry'.¹⁰ This population was chosen for its contemporary and observational aspects to best represent an appropriate control for our North American study population. For our COVID-19 comparison, we selected the Global COVID-19 Stroke Registry¹¹ as some of our centres were previously included in contemporaneous North American registries therefore could not serve as an effective control due to overlap.¹¹ Finally, for our LVO cohorts, we chose the interventional and non-interventional arms of a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands (MR CLEAN).¹² MR CLEAN had the most broadly defined inclusion criteria of all endovascular randomised controlled trials and most closely mimicked the real-life constraints in endovascular stroke care experienced during the pandemic.

Statistical analysis

Patient baseline demographics were illustrated using descriptive statistics. Categorical variables were presented as frequencies and percentages and compared by χ^2 or Fisher's exact test as appropriate. Continuous variables were presented as median and IQR. The normality of the data was tested using histograms and confirmed by the Shapiro-Wilk test. Univariable and multivariable mixed effects ordinal (mRS) and binary (all other outcomes) logistic regression analyses were conducted to evaluate for determinants of primary and secondary outcomes. The variables included in the univariable analysis were age, sex, race, comorbidities (hypertension, diabetes mellitus, etc), admission NIHSS, LVO, aetiology, NLR, D-dimer, absolute lymphocyte count, platelet count, IV tPA, mechanical thrombectomy and presence of sICH. Of those, variables with prespecified p values < 0.1 in univariable analysis were included in the multivariable model. Spearman rank correlation and variance inflation factors (VIF) were used to detect multicollinearity. High multi-collinearity was defined as a Spearman's rho > 0.8 or a VIF > 5 , and variables with high multi-collinearity were excluded from the multivariable model. Multiple imputation using chained equations was done to account for missing data. The imputation model included the variables in the multivariable analysis, centres and mRS score or mortality at discharge. Overall, 20 datasets were imputed, and the models were built on each of the 20 datasets, and then the results were pooled according to Rubin's rules. All analyses were performed using Stata (V.16.0, StataCorp) and R (V.4.0.2, Vienna, Austria). All tests were two sided, and p values < 0.05 were considered statistically significant.

Patient and public involvement

No patients or members of the public were involved in the conceptualisation or design of this study, nor in the interpretation of the results.

RESULTS

Characteristics and outcomes of the study population

This study involved 216 AIS consecutive patients who tested positive for SARS-CoV-2. There were 68.1% (147/216) patients who were older than 60 years while 31.9% (69/216) were younger. The female-to-male ratio was 1:1.2. A majority of the patients were African American (46.2%, 91/197). The most common comorbidity was hypertension (80.0%, 172/215), followed by hyperlipidaemia (47.8%, 96/201) and diabetes mellitus (47.6%, 100/210). Fever (temperature >99° Fahrenheit/38° Celsius) was present in 29.6% (64/216) of the patients at presentation. Severe COVID-19 inflammation has present in 56.9% (74/130). Hypercoagulability was present in 33.1% (49/148) of patients. The median (IQR) of NIHSS at admission was 12.5 (15.8) (n=170) and 44.2% (87/197) of the patients presented with LVO.

No significant differences in median NIHSS (IQR) at admission (12.0 (15.8) vs 13.5 (15.3), $p=0.264$) or rates of LVO (41.5%, 54/130 vs 49.3%, 33/67, $p=0.302$) were observed between older age patients (≥ 60 years) in comparison to younger ones, respectively. CS/ESUS (38.0%, 52/137: CS=2%, 3/137 and ESUS=36%, 49/137) and cardioembolism (36.5%, 50/137) were the most common stroke aetiologies. Other variables including COVID-19 symptoms at presentation, laboratory findings on admission and management of these patients are detailed in table 1. IV tPA was given to 19.0% (39/205) and 20.8% (40/192) received mechanical thrombectomy.

Poor outcomes at discharge were observed in 51.3% (98/191) of the patients, while 17.8% (34/191) had favourable outcomes at discharge (table 2, figure 1A). Figure 1B,C shows the distribution of mRS score based on hypercoagulability (by D-dimer level) and the severity of COVID-19 (by NLR level). Symptomatic intracranial haemorrhage was reported in 8.3% (18/216) of the patients. Of sICH cases, 40% (n=7) were seen in those who received acute therapy: one with tPA, two with both tPA and thrombectomy and four who underwent thrombectomy alone. Another 60% (n=11) were those who did not receive any treatment with a majority (8/11) being non-LVO cases. The mortality at discharge was 39.1% (81/207).

Determinants of clinical outcome

Age, diabetes mellitus, NIHSS at admission, LVO, NLR, stroke aetiology and sICH were identified as determinants of poor outcomes in univariable analyses (table 3). In the multivariable analysis, older age (≥ 60 years) (adjusted OR (aOR): 5.11, 95% CI 2.08 to 12.56, $p<0.001$), diabetes mellitus (aOR: 2.66, 95% CI 1.16 to 6.09, $p=0.021$), higher NIHSS at admission (aOR: 1.08, 95% CI 1.02 to 1.14, $p=0.006$), LVO (aOR: 2.45, 95% CI 1.04 to 5.78, $p=0.042$), and higher NLR level (aOR: 1.06, 95% CI 1.01 to 1.11, $p=0.028$) were significantly associated with poor outcome. The results of the multicollinearity assessment showed no substantial correlation between these determinants.

The results of the univariable mixed effects ordinal logistic regression analyses for determinants of a reduction in mRS score and decreased disability are detailed in table 4. In the multivariable analysis, older age (aOR: 0.31, 95% CI 0.15 to 0.66, $p=0.003$), diabetes mellitus (aOR: 0.47, 95% CI 0.23 to 0.94, $p=0.032$), higher NIHSS at admission (aOR: 0.91, 95% CI 0.87 to 0.96, $p<0.001$), higher NLR (aOR: 0.95, 95% CI 0.91 to 0.99, $p=0.008$), and sICH (aOR:

Table 1 Baseline characteristics, labs and treatments (n=216)

	N	Values
Age categories (in years)	216	
<60		69 (31.9%)
≥ 60		147 (68.1%)
Sex	216	
Male		118 (54.6%)
Female		98 (45.4%)
Race	197	
African-American		91 (46.2%)
Caucasian		63 (32.0%)
Others		43 (21.8%)
Comorbidities		
Smoking	187	26 (13.9%)
Atrial fibrillation	208	31 (14.9%)
Prior anticoagulation	121	17 (14.0%)
Coronary artery disease	212	39 (18.4%)
Congestive heart failure	206	37 (18.0%)
Diabetes mellitus	210	100 (47.6%)
Hypertension	215	172 (80.0%)
Hyperlipidaemia	201	96 (47.8%)
Previous stroke	205	47 (22.9%)
Peripheral vascular disease	110	3 (2.73%)
Chronic kidney disease	201	46 (22.9%)
Presentation		
Fever	216	64 (29.6%)
Cough	216	71 (32.9%)
Dyspnoea	216	59 (27.3%)
Nausea or vomiting	216	14 (6.48%)
chest pain	216	14 (6.51%)
Sore throat	216	14 (6.48%)
Asymptomatic	216	44 (20.37%)
Awareness of COVID-19 prior to stroke admission	105	47 (44.8%)
Severe COVID-19 inflammation (NLR ≥ 4.5)	130	74 (56.9%)
Very severe COVID-19 inflammation (NLR ≥ 6.5)	130	57 (43.8%)
Hypercoagulability (D-dimer ≥ 1000 ng/mL)	148	49 (33.1%)
Severe hypercoagulability (D-dimer ≥ 2000 ng/mL)	148	37 (25.0%)
Admission NIHSS	170	12.5(15.8)
Large vessel occlusion	197	87 (44.2%)
Stroke aetiology	137	
Cardioembolism		50 (36.5%)
CS/ESUS		52 (38.0%)
Large-artery atherosclerosis		19 (13.9%)
Small-vessel occlusion		16 (11.7%)
Labs		
NLR	130	5.00 (8.00)
D-dimer (ng/mL)	148	22.0 (1920)
INR	174	1.10 (0.280)
aPTT (s)	56	30.4 (6.60)
C reactive protein (mg/dL)	152	17.6 (50.6)
Ferritin (ng/mL)	158	478 (675)
White cell count (1000/ μ L)	199	8.41 (4.51)
Absolute neutrophil (1000/ μ L)	130	6.30 (4.15)
Absolute lymphocyte (1000/ μ L)	173	1.20 (0.800)
Platelets	180	227 (127)
Creatinine (mg/dL)	184	1.12 (0.933)
LDH (U/L)	122	353 (370)
Triglycerides (mg/dL)	131	128 (84.0)

Continued

Table 1 Continued

	N	Values
Troponin (ng/mL)	108	0.0300 (0.228)
LDL (mg/dL)	128	84.0 (52.8)
Haemoglobin(Hg)A1c (%)	130	6.30 (2.85)
Aspirin	120	80 (66.7%)
Plavix	108	27 (25.0%)
Heparin	127	35 (27.6%)
Low dose enoxaparin	124	41 (33.1%)
High dose enoxaparin	120	2 (1.67%)
IV tPA	205	39 (19.0%)
Thrombectomy	192	40 (20.8%)

Continuous variables are presented as median (range).

aPTT, activated partial thromboplastin time; CPK, creatine phosphokinase; CS/ESUS, cryptogenic stroke/embolic stroke of undetermined source; ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; INR, international normalised ratio; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil-lymphocyte ratio; IV tPA, intravenous tissue plasminogen activator.

0.18, 95% CI 0.04 to 0.73, $p=0.016$) were significantly associated with fewer instances of mRS score reduction and increased chance of disability at discharge.

Table 5 shows the results of the univariable mixed effects binary logistic regression analyses for determinants of mortality. This multivariable analysis identified older age (aOR: 3.54, 95% CI 1.46 to 8.55, $p=0.005$), diabetes mellitus (aOR: 2.68, 95% CI 1.25 to 5.74, $p=0.012$), higher NIHSS at admission (aOR: 1.06, 95% CI 1.02 to 1.12, $p=0.009$), LVO (aOR: 3.23, 95% CI 1.40 to 7.46, $p=0.006$), higher NLR (aOR: 1.07, 95% CI 1.02 to 1.13, $p=0.009$) and sICH (aOR: 6.41, 95% CI 1.74 to 23.67, $p=0.005$) as significant determinants of increased mortality.

Stratified analysis using determinants of severity for inflammation (NLR) and hypercoagulability (D-dimer) revealed that there

Table 2 Outcomes of the included patients (n=216)

	N	Values (%)
Post-thrombectomy mTICI	35	
0		2 (5.71)
1		1 (2.86)
2a		5 (14.3)
2b		11 (31.4)
3		16 (45.7)
In-hospital system complications		
Pulmonary	216	59 (27.31)
Cardiac	216	24 (11.11)
Renal	216	39 (18.06)
Deep vein thrombosis	216	8 (3.70)
Discharge mRS	191	
0		12 (6.28)
1		10 (5.24)
2		12 (6.28)
3		23 (12.0)
4		36 (18.8)
5		17 (8.90)
6		81 (42.4)
Symptomatic intracerebral haemorrhage	216	18 (8.33)
Mortality	207	81 (39.1)

mRS, modified Rankin Scale; mTICI, modified treatment in cerebral infarction; sICH, symptomatic intracranial haemorrhage.

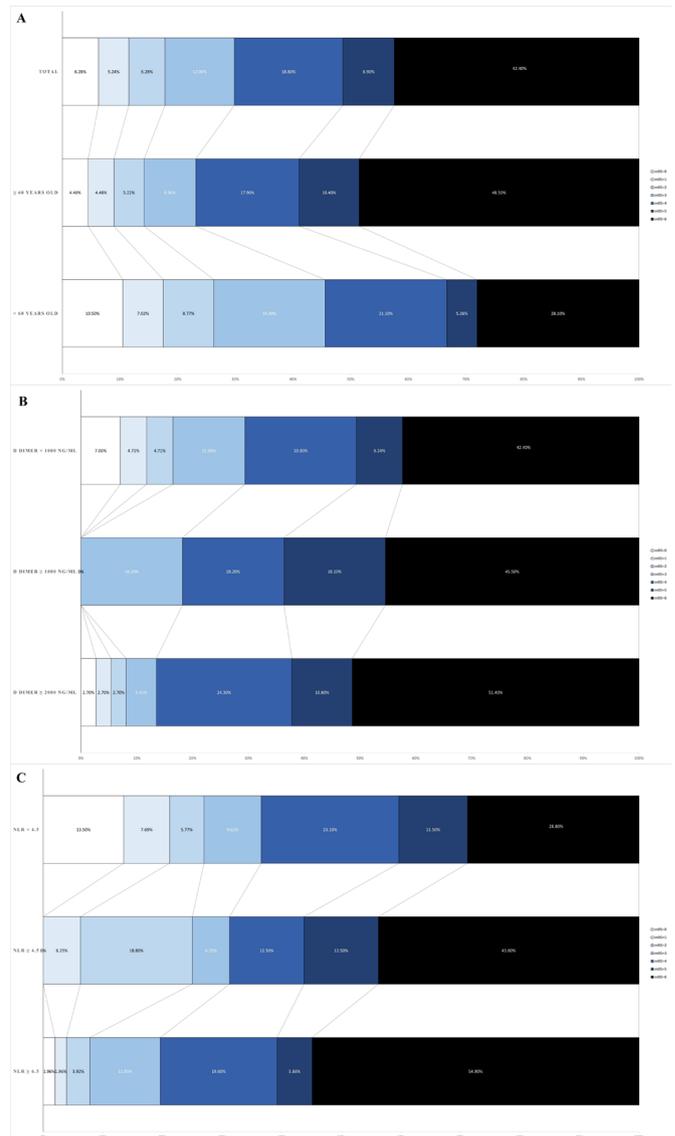


Figure 1 Gotta bar for mRS scores in: (A) the total sample based on age; (B) the severity of COVID-19 inflammation; and (C) hypercoagulability. mRS, modified Rankin Scale.

was a higher mortality in the former group for patients with severe and very severe levels of inflammation ($p=0.048$), but this relationship was not observed to be significant with hypercoagulability (figure 2). This was also seen in the multivariable analyses where an increase in NLR but not D-dimer correlated with both outcome and mortality. We did not find any substantial correlation between NLR and D-dimer levels (Spearman's $\rho=0.13$).

Comparison with other studies

Comparative analysis of our COVID-AIS data (online supplemental table 1) with previous non-COVID ischaemic stroke data (GWTG Stroke data) showed that patients in our study had higher mortality (39.1% vs 4.8%, $p<0.01$) as well as lower likelihood of favourable outcome based on mRS score at discharge (17.8% vs 39.5%, $p<0.01$). This was also seen in comparative analysis of our respective LVO cohorts with the MR CLEAN study population. Both thrombectomy (37.8% vs 11.6%, $p<0.001$) and non-thrombectomy (58.7% vs 12.4%, $p<0.01$) LVO groups in our study had higher rates of mortality. Mortality

Table 3 Determinants of poor outcomes (mRS 5–6) (n=216)

	Poor outcome (mRS score 5–6)					
	Univariable			Multivariable*		
	OR	95% CI	P value	OR	95% CI	P value
Age (years)						
<60		Ref			Ref	
≥60	2.87	1.50 to 5.50	0.001	5.11	2.08 to 12.56	<0.001
Sex						
Female		Ref				
Male	1.03	0.58 to 1.82	0.916			
Race						
African-American		Ref				
Caucasian	0.67	0.34 to 1.32	0.245			
Others	1.23	0.56 to 2.74	0.606			
Comorbidities						
Smoking	1.20	0.48 to 2.99	0.702			
Atrial fibrillation	0.65	0.29 to 1.46	0.300			
Prior anticoagulation	0.40	0.11 to 1.50	0.175			
Coronary artery disease	1.22	0.58 to 2.57	0.604			
Congestive heart failure	1.40	0.65 to 3.05	0.390			
Diabetes mellitus	2.26	1.26 to 4.07	0.006	2.66	1.16 to 6.09	0.021
Hypertension	1.46	0.73 to 2.93	0.286			
Hyperlipidaemia	0.93	0.52 to 1.68	0.819			
Previous stroke	0.96	0.48 to 1.91	0.904			
Chronic kidney disease	1.05	0.52 to 2.14	0.887			
Admission NIHSS (one unit)	1.10	1.06 to 1.15	<0.001	1.08	1.02 to 1.14	0.006
Large vessel occlusion	3.02	1.63 to 5.59	<0.001	2.45	1.04 to 5.78	0.042
Stroke aetiology						
Cardioembolism	Ref			Ref		
CS/ESUS	0.96	0.42 to 2.20	0.926	1.35	0.39 to 4.68	0.636
Large-artery atherosclerosis	1.56	0.52 to 4.69	0.427	2.22	0.54 to 9.09	0.264
Small-vessel occlusion	0.22	0.05 to 1.15	0.073	0.21	0.03 to 1.54	0.123
Labs						
NLR (one unit)	1.07	1.01 to 1.13	0.025	1.06	1.01 to 1.11	0.028
D-dimer (×100 ng/mL)	1.01	1.00 to 1.02	0.101			
Absolute lymphocyte (1000/μL)	1.01	0.99 to 1.02	0.727			
Platelets	1.00	1.00 to 1.00	0.435			
IV tPA	0.56	0.27 to 1.15	0.115			
Thrombectomy	0.77	0.38 to 1.57	0.469			
sICH	3.10	0.96 to 10.0	0.058	3.63	0.85 to 15.48	0.081

Univariable and multivariable mixed effects binary logistic regression analyses were done to test for the impact of several determinants on getting poor outcomes. Variables that had a p<0.1 were included in the final multivariable model.

*The results after multiple imputation using chained equations to handle missing data.

CS/ESUS, cryptogenic stroke/embolic stroke of undetermined source; IV tPA, intravenous tissue plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil–lymphocyte ratio; sICH, symptomatic intracranial haemorrhage.

was also worse in our North American cohort compared with data reported in the Global COVID-19 Stroke Registry (39.1% vs 27.6%, p=0.018).¹¹

DISCUSSION

This is the largest North American cohort of patients hospitalised with AIS and concurrent SARS-CoV-2 infection, which aimed to determine the factors that predict the outcomes in COVID-19 patients with AIS. The most critical finding of our study is the relationship between COVID-19 associated AIS and severe disability or death. We observed these poor outcomes (mRS 5–6) in approximately 51% of our cohort, with an in-hospital/discharge mortality of 39.1%, both of which are high compared with historic data.¹² This relationship seems to ring true when we use historical controls of either all-cause ischaemic

stroke (non-COVID) or LVOs. We found that mortality was significantly higher than the Get With the Guidelines (GWTG) non-COVID ischaemic cohort (39.1% vs 27.6%) or when compared with the respective LVO study arms in MR CLEAN (37.8% vs 11.6%).^{10 12} The North American cohort of our consortium (n=216) fared worse than the comparable global cohort (n=174) of Ntaios *et al*¹¹ in terms of both morbidity and mortality. Conversely, we also observed lower rates of favourable outcomes (mRS 0–2) compared with the GWTG non-COVID ischaemic cohort (17.8% vs 39.5%).¹⁰

We identified advanced age (≥60), diabetes mellitus, higher NLR, higher admission NIHSS, presence of LVO and occurrence of sICH as predictors of mortality. These are consistent with previous studies in AIS patients without COVID-19.¹³ While

Table 4 Determinants of mRS score reduction (n=216)

	mRS score reduction (shift analysis)					
	Univariable			Multivariable*		
	OR	95% CI	P value	OR	95% CI	P value
Age (years)						
<60		Ref			Ref	
≥60	0.39	0.22 to 0.69	0.001	0.31	0.15 to 0.66	0.003
Sex						
Female		Ref			Ref	
Male	1.11	0.67 to 1.86	0.682			
Race						
African-American		Ref			Ref	
Caucasian	1.57	0.84 to 2.92	0.157			
Others	0.86	0.41 to 1.80	0.688			
Comorbidities						
Smoking	0.63	0.25 to 1.58	0.323			
Atrial fibrillation	1.38	0.69 to 2.79	0.365			
Prior anticoagulation	1.42	0.53 to 3.79	0.483			
Coronary artery disease	1.00	0.52 to 1.92	0.990			
Congestive heart failure	0.79	0.40 to 1.57	0.500			
Diabetes mellitus	0.44	0.26 to 0.74	0.002	0.47	0.23 to 0.94	0.032
Hypertension	0.56	0.29 to 1.06	0.074	0.66	0.29 to 1.49	0.315
Hyperlipidaemia	1.04	0.61 to 1.77	0.880			
Previous stroke	1.11	0.59 to 2.08	0.745			
Chronic kidney disease	1.01	0.52 to 1.93	0.987			
Admission NIHSS (one unit)	0.89	0.86 to 0.93	<0.001	0.91	0.87 to 0.96	<0.001
Large vessel occlusion	0.34	0.19 to 0.59	<0.001	0.52	0.23 to 1.20	0.124
Stroke aetiology						
Cardioembolism		Ref			Ref	
CS/ESUS	1.23	0.59 to 2.56	0.576	1.19	0.52 to 2.73	0.685
Large-artery atherosclerosis	0.98	0.36 to 2.67	0.964	0.89	0.29 to 2.77	0.843
Small-vessel occlusion	2.92	0.99 to 8.59	0.052	2.98	0.71 to 12.44	0.131
Labs						
NLR (one unit)	0.92	0.86 to 0.98	0.007	0.95	0.91 to 0.99	0.008
D dimer (μ100 ng/mL)	0.99	0.99 to 1.00	0.081	0.99	0.98 to 1.00	0.093
Absolute lymphocyte (1000/μL)	1.00	0.99 to 1.01	0.804			
Platelets	1.00	1.00 to 1.00	0.536			
IV tPA	1.60	0.86 to 2.97	0.137			
Thrombectomy	1.04	0.55 to 1.98	0.898			
sICH	0.23	0.07 to 0.76	0.015	0.18	0.04 to 0.73	0.016

Univariable and multivariable mixed effects ordinal logistic regression analyses were done to test for the impact of several determinants on a reduction of mRS score and a decrease in disability. Variables that had a p<0.1 were included in the final multivariable model.

*The results after multiple imputation using chained equations to handle missing data.

CS/ESUS, cryptogenic stroke/embolic stroke of undetermined source; NIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil-lymphocyte ratio; sICH, symptomatic intracranial haemorrhage; IV tPA, intravenous tissue plasminogen activator.

worsening severity of inflammation (as determined by NLR) was seen to predict both morbidity and mortality, D-dimer did not seem to have the same effect. We also did not find a correlation between markers of inflammation and hypercoagulability. This is an interesting finding and has not been reported previously in either COVID-19 related stroke or hypercoagulability literature. This may in turn explain why higher prophylactic anticoagulation targets may have not altered mortality in many COVID-19 related cases.¹⁴

Interestingly, a large proportion of patients in our cohort had African-American background (46.2%). This has been similarly noted by Qureshi *et al*,¹⁵ who analysed data from 54 centres comprising 8163 patients with COVID-19. The authors found that in their cohort, African-American patients accounted for

44.7% of cases of stroke with COVID-19. The reasons underlying this observation are multifactorial and complex and could not be further analysed on the limited granularity of data available. It is likely related to factors including structural racism and social determinants of health, where patients are more likely to be uninsured, have suboptimal access to timely medical care and may have higher rates of pre-existing and underlying health conditions,^{16 17} all factors that may be exacerbated in crisis times like the COVID-19 pandemic.

The presence of concurrent SARS-CoV-2 infection appears to complicate the relationship between age and AIS. Advanced age has been shown to be a robust and non-modifiable predictor of outcomes in both short-term and long-term analyses.^{13 18} Despite age being a significant predictor of poor outcome in our cohort,

Table 5 Determinants of mortality (n=216)

	Mortality					
	Univariable			Multivariable*		
	OR	95% CI	P value	OR	95% CI	P value
Age (years)						
<60		Ref			Ref	
≥60	2.41	1.25 to 4.67	0.009	3.54	1.46 to 8.55	0.005
Sex						
Female		Ref			Ref	
Male	0.75	0.42 to 1.34	0.334			
Race						
African-American		Ref			Ref	
Caucasian	0.64	0.30 to 1.37	0.253			
Others	1.30	0.57 to 2.98	0.534			
Comorbidities						
Smoking	1.92	0.73 to 5.07	0.186			
Atrial fibrillation	0.80	0.34 to 1.85	0.599			
Prior anticoagulation	0.64	0.17 to 2.43	0.509			
Coronary artery disease	0.81	0.37 to 1.75	0.592			
Congestive heart failure	1.01	0.47 to 2.20	0.975			
Diabetes mellitus	2.46	1.38 to 4.37	0.002	2.68	1.25 to 5.74	0.012
Hypertension	1.19	0.58 to 2.44	0.637			
Hyperlipidaemia	0.93	0.52 to 1.68	0.815			
Previous stroke	0.97	0.49 to 1.95	0.938			
Chronic kidney disease	1.11	0.51 to 2.38	0.794			
Admission NIHSS (one unit)	1.09	1.05 to 1.13	<0.001	1.06	1.02 to 1.12	0.009
Large vessel occlusion	3.10	1.68 to 5.70	<0.001	3.23	1.40 to 7.46	0.006
Stroke aetiology						
Cardioembolism		Ref			Ref	
CS/ESUS	0.86	0.37 to 2.00	0.721			
Large-artery atherosclerosis	1.09	0.36 to 3.32	0.875			
Small-vessel occlusion	0.29	0.06 to 1.44	0.130			
Labs						
NLR (one unit)	1.08	1.01 to 1.15	0.020	1.07	1.02 to 1.13	0.009
D dimer (×100 ng/mL)	1.01	1.00 to 1.02	0.129			
Absolute lymphocyte (1000/μL)	0.97	0.90 to 1.04	0.335			
Platelets	1.00	1.00 to 1.00	0.547			
IV tPA	0.53	0.23 to 1.23	0.139			
Thrombectomy	0.87	0.42 to 1.81	0.712			
sICH	3.56	1.25 to 10.16	0.017	6.41	1.74 to 23.67	0.005

Univariable and multivariable mixed effects binary logistic regression analyses were done to test for the impact of several determinants on mortality. Variables that had a $p < 0.1$ were included in the final multivariable model.

*The results after multiple imputation using chained equations to handle missing data.

CS/ESUS, cryptogenic stroke/embolic stroke of undetermined source; NIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil-lymphocyte ratio; sICH, symptomatic intracranial haemorrhage; IV tPA, intravenous tissue plasminogen activator.

12.5% of our cases were under the age of 50 years. While this proportion of young ischaemic stroke is consistent with recent epidemiological data (10%–15%), nearly half (48.2%) of our young stroke cases were secondary to LVOs.¹⁹ Several other studies on AIS and COVID-19 have also shown a higher proportion of LVO presentations in young adults.^{20–21} The reasons for the trend observed where younger patients experience AIS and tend to have LVO is not well established. It is hypothesised that increased hypercoagulable state^{22–23} in younger patients may lead to increased risk of AIS LVO strokes, and given their lack of other comorbidities and greater physiological reserve, their outcomes if treated in an optimal and timely manner may be better than those of their elderly counterparts. While the risk of LVO is high in patients with younger age, we found no significant

difference in rates of LVO between older and younger patients, which suggests that the risk of LVO is generally increased with COVID-19 and does not necessarily only affect younger ones.

It has been suggested that the proportion of LVO may be higher in AIS patients with COVID-19 infection, given the propensity to develop thrombotic complications, particularly in patients with severe clinical course.²⁴ Prior analyses on stroke prevalence in the general population report proportions of patients presenting with LVO between 24% and 46%, depending on the authors' definition of a 'large vessel'.^{25–26} In our cohort, approximately 44% patients presented with LVO, and presence of an LVO was associated with increased disability and mortality. The relatively high proportion of LVO strokes in our study may be related to the relatively high frequency of thrombotic complications in

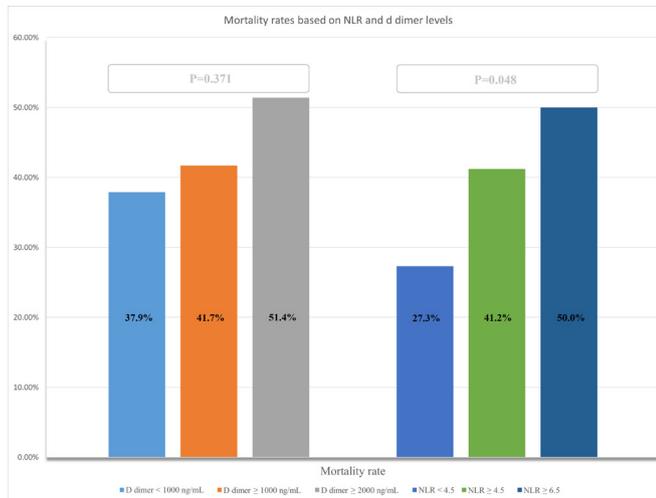


Figure 2 Stratified analysis for mortality using determinants of severity for inflammation (NLR) and hypercoagulability (D-dimer). NLR, neutrophil-to-lymphocyte ratio.

patients with COVID-19.²⁴ A recent systematic review analysing clinical phenotype in COVID-19 associated AIS reported a similarly high proportion of LVO (46.9%), suggesting this finding is less likely an artefact of selection.²⁷

It remains uncertain to what extent or through which mechanisms SARS-CoV-2 infection is contributing to LVO frequency and poor functional outcomes. Active infection acts as a catalyst for the occurrence of AIS, as the proinflammatory response against a pathogen can precipitate stroke through several inter-related pathogenesis, in addition to other neurological complications.²⁸ This observation is supported by studies that have demonstrated a short-term increased risk of AIS in patients who had a recent influenza-like illness, systemic respiratory illness, hospitalisation with infection and sepsis prior to occurrence of AIS.^{29–33} However, Fridman *et al* report that the observed risk of AIS in a meta-analysis of patients with COVID-19 is higher than those observed in severe sepsis (1.6% vs 0.78%) and higher than in those patients with influenza (1.6% vs 0.2%).^{27, 33} In studies analysing those with recent sepsis or influenza-like illness, an age interaction was observed, whereby the increase in AIS risk was disproportionately higher in younger patients.^{29, 32} The higher proportion of AIS in young adults attributable to underlying hypercoagulability may be the common pathophysiology that underpins the observed phenomenon in patients with COVID-19 and other infectious agents. Similar observations have been made with respect to thrombotic complications associated with SARS-CoV-1 and H1N1 influenza outbreaks.^{34, 35}

Our study has several limitations. Although our goal was to gather a broad range of clinical and diagnostic variables, we found some heterogeneity in patient records, resulting in variably complete data acquisition. Second, our study sample was restricted to patients seeking hospital care. Our patient cohort might therefore be biased towards more severe COVID-19 infections and the results of this study may not be generalisable to all COVID-19 positive patients. Additionally, our cohort did not have a prospectively monitored control group. Some parameters including viral load, cardiac and pulmonary comorbidity severity were not available for analysis and thus limits our assessment of the influence of these factors on patient outcome. We were not able to assess COVID-19 severity and its impact on stroke outcomes. We also acknowledge that the NLR is not the perfect marker for COVID-19 inflammation and, indeed, NLR may be

increased in stroke without COVID-19 and has also been used as a prognostic marker for those patients as well. Finally, several factors that were not captured in this study, such as socioeconomic status, local healthcare infrastructure and resources, as well as local support networks that may have contributed to the clinical outcomes we observed.

CONCLUSION

In this North American cohort, we found that patients who sustain AIS in the setting of COVID-19 may potentially suffer poorer outcomes proportionate to the severity of infection in addition to other contributing factors that are known to modulate outcomes in AIS, with worse outcomes compared with historic controls or global COVID-19 AIS averages. If further investigations into COVID-19 related thrombogenesis reiterate this trend, they may lay a foundation to understanding future infection or inflammation-induced hypercoagulability, especially in immunological thrombophilia.

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