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4C Mortality Score correlates with in-hospital functional outcome after COVID-19-associated ischaemic stroke

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ABSTRACT

Aim of the study. The 4C Mortality Score was created to predict mortality in hospitalised patients with COVID-19 and has to date been evaluated only in respiratory system disorders. The aim of this study was to investigate its application in patients with COVID-19-associated acute ischaemic stroke (AIS).

Clinical rationale for study. COVID-19 is a risk factor for AIS. COVID-19-associated AIS results in higher mortality and worse functional outcome. Predictors of functional outcome in COVID-19-associated AIS are required.

Materials and methods. This was a retrospective observational study of patients with AIS hospitalised in seven neurological wards in Małopolska Voivodship (Poland) between August and December 2020. We gathered data concerning the patients' age, sex, presence of cardiovascular risk factors, type of treatment received, and the presence of stroke-associated infections (including pneumonia, urinary tract infection and infection of unknown source). We calculated 4C Mortality Score at stroke onset, and investigated whether there was a correlation with neurological deficit measured using the National Health Institute Stroke Scale (NIHSS) and functional outcome assessed using the modified Rankin Scale (mRS) at discharge.

Results. The study included 52 patients with COVID-19-associated AIS. The 4C Mortality Score at stroke onset correlated with mRS ($r_s = 0.565$, $p < 0.01$) at discharge. There was also a statistically significant difference in the mean 4C Mortality Score between patients who died and patients who survived the stroke (13.08 ± 2.71 *vs.* 9.85 ± 3.47, $p = 0.04$).

Conclusions and clinical implications. 4C Mortality Score predicts functional outcome at discharge in COVID-19-associated AIS patients.

Key words: acute ischaemic stroke, COVID-19, 4C Mortality Score, modified Rankin Scale

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Introduction

As the COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread across the globe, researchers found growing evidence that several neurological conditions, including stroke, are associated with the disease [1].

A recent systematic review and meta-analysis has shown that acute cerebrovascular disease occurs in about 1.4% of all COVID-19 patients (ranging from 0.4% to 8.1% in different observational cohort studies) [2]. Acute ischaemic stroke (AIS) is the most common cerebrovascular complication of SARS-CoV-2 infection, but cases of COVID-19-associated haemorrhagic stroke and cerebral venous thrombosis have also been described in the literature [3, 4].

SARS-CoV-2 infection is proven to be an independent risk factor for AIS [5]. The suggested mechanisms in which SARS-CoV-2 increases the risk of AIS are hypercoagulation, vasculitis and cardiomyopathy. Various laboratory markers of coagulopathy are found in patients with COVID-19, including elevated D-dimer levels and abnormalities in prothrombin time, platelet count or fibrinogen level; the presence of antiphospholipid antibodies has been detected in some patients, although their impact remains uncertain. Because angiotensin-converting enzyme 2 (ACE2) receptors, through which SARS-CoV2 enters the cells, are also present in the vascular endothelium, the virus can affect them causing lymphocytic endothelitis. Cardiomyopathy can be a direct effect of viral infection or can occur due to concomitant inflammation or hypoxia [6, 7]. Recent studies show that cases of AIS in patients with COVID-19 are more severe at onset [8] and result in higher mortality and worse functional outcome [9].

The 4C Mortality Score is a validated tool for predicting mortality in hospitalised patients with COVID-19 [10], but no studies have been performed thus far to assess its application in patients with COVID-19-associated AIS.

Clinical rationale for study

The aim of this study was to determine whether 4C Mortality Score calculated at the onset of COVID-19-associated AIS could be a predictor of in-hospital death, and whether it correlated with neurological deficit and functional outcome at discharge. As SARS-CoV-2 is highly infectious and spreads quickly across different communities, the coming months may increase the burden of COVID-19-associated ischaemic stroke cases, meaning that there is an urgent need for research on prognostic tools in AIS patients.

Materials and methods

In this retrospective observational study, we analysed the medical documentation of patients diagnosed with stroke who were hospitalised in seven neurological wards in five cities in Małopolska Voivodship (Poland) between 14 August and 16 December 2020.

The study included patients with AIS associated with COVID-19 infection, confirmed by detecting SARS-CoV-2 RNA by reverse transcription polymerase chain reaction (RT-PCR) from a nasopharyngeal swab.

We considered AIS to be associated with COVID-19 in three cases:

1. AIS in a patient with ongoing symptomatic COVID-19 infection confirmed before admission
2. AIS in a patient without symptoms of infection with a positive SARS-CoV-2 test on admission
3. AIS in a patient with a positive SARS-CoV-2 test obtained during hospitalisation in the stroke unit with no potential source of infection on that ward.

The 4C Mortality Score was calculated on admission for each patient. This score ranges from 0 to a possible 21 points and it includes eight parameters: age, gender, number of comorbidities, peripheral oxygen saturation, respiratory rate, level of consciousness (assessed using the Glasgow Coma Scale) and results of laboratory tests: serum urea and C-reactive protein levels [10].

Each patient was followed according to the standard protocol of the Krakow Stroke Data Bank, a single-centre registry of clinical, radiological and genetic data of hospitalised patients with AIS. For the purposes of this study, we analysed the presence of cardiovascular risk factors (Tab. 1) and concomitant stroke-associated infections requiring antibiotic therapy including pneumonia, urinary tract infection and infections of unknown source. We also noted the type of treatment i.e. intravenous thrombolysis (IVT), mechanical thrombectomy (MT), or no reperfusion therapy. We collected data concerning in-hospital mortality, neurological deficit measured in the National Institute of Health Stroke Scale (NIHSS) at discharge,

Table 1. Frequency of cardiovascular risk factors and stroke-associated infections requiring antibiotic therapy in patients with COVID-19-associated AIS

Cardiovascular risk factor	N (%)
Arterial hypertension	43/52 (83%)
Diabetes mellitus	19/52 (37%)
Atrial fibrillation	19/52 (37%)
Coronary artery disease	16/52 (31%)
Overweight/obesity	12/52 (23%)
History of stroke/TIA	9/52 (17%)
Dyslipidemia	9/52 (17%)
History of smoking	9/52 (17%)
Peripheral arterial disease	8/52 (15%)
Carotid artery atherosclerosis	30/40 (75%)
Stroke-associated infections requiring antibiotic therapy	**N (%)**
Pneumonia	17/52 (33%)
Pneumonia + urinary tract infection	4/52 (8%)
Infection of unknown source	9/52 (17%)

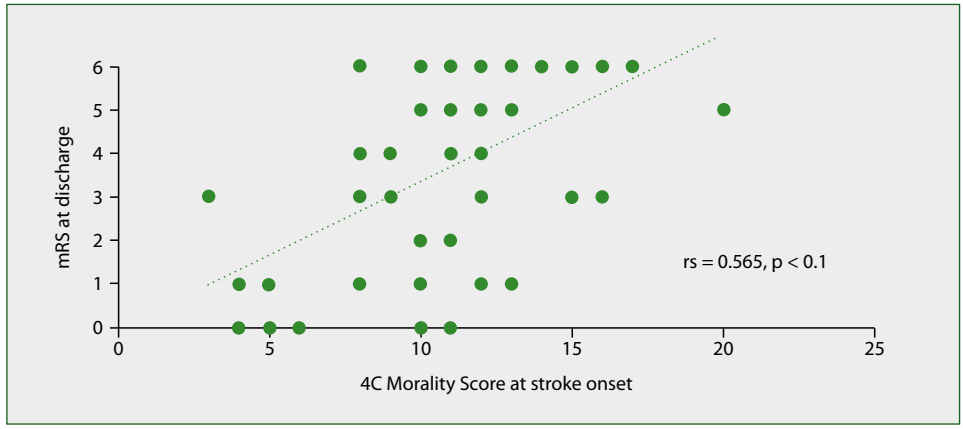

Figure 1. Scatterplot showing results of mRS at discharge in patients with different 4C Mortality Score results at stroke onset with trendline

and functional outcome at discharge assessed with the modified Rankin Scale (mRS).-

The data we collected was put into a database and analysed using a PS Imago Pro 6.0 program. Categorical data was presented as counts and percentages, and continuous data as mean and standard deviation (SD) or median and interquartile range (IQR). Continuous variables were tested for normality using a Shapiro-Wilk test and compared between groups by a Mann-Whitney U test. The correlations between continuous variables were assessed using Spearman's rank-order correlation. A p-value of less than 0.05 (two-sided) was considered to be statistically significant.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Bioethics Committee of the District Medical Council in Krakow (opinion number 143/KBL/OIL/2020).

Results

We identified 60 patients with COVID-19-associated stroke: 54 (90%) with AIS, five (8%) with haemorrhagic stroke, and one (2%) with cerebral venous thrombosis. Seventeen (31%) patients with COVID-19-associated AIS received reperfusion therapy: 12 (22%) were treated with IVT, two (3.5%) with MT, and three (5.5%) with both methods.

In one patient with AIS there was no follow-up available regarding neurological outcome because they had been transferred to another hospital. In one patient calculation of 4C Mortality Score at stroke onset was impossible because they had been hospitalised in another centre and the documentation data was incomplete. Therefore, the final analysis included 52 patients with COVID-19-associated AIS.

The patients were aged 49 to 97 years with a mean age of 75 (SD = 10.8). 32 of them (61.5%) were male. Forty-six patients (88%) had at least two concomitant cardiovascular risk factors. The most common risk factor was arterial hypertension (N = 43, 83%) (Tab. 1). The presence of carotid artery atherosclerosis could be assessed in 40 patients (in others the diagnostics of stroke causes was performed after discharge from a COVID ward, and they were lost to follow-up), and it was present in 30 (75%) of those 40 patients.

A concomitant infection requiring antibiotic use was present in 30 (58%) patients: pneumonia in 17 patients (33%), both pneumonia and urinary tract infection in four (8%), and nine patients (17%) received antibiotics due to infection of unknown source. Seven (13%) patients were diagnosed with viral pneumonia due to COVID-19 and did not receive antibiotic therapy.

The 4C Mortality Score at the onset of stroke varied from 3 to 20 points with a median of 11 (IQR = 4).

The mortality rate in our group was 23% (N = 12). There was a significant difference in the mean 4C Mortality Score between patients who died and patients who survived the stroke (13.08 ± 2.71 *vs.* 9.85 ± 3.47, p = 0.04).

There was a statistically significant ($p < 0.01$) moderate positive correlation between 4C Mortality Score and the in-hospital functional outcome after stroke assessed with mRS (Spearman's Rank Correlation Coefficient = 0.565). For a scatterplot showing results of mRS at discharge in patients with different 4C Mortality Score results at onset, see Figure 1.

The correlation between 4C Mortality Score and the neurological deficit at discharge measured using the NIHSS scale was also statistically significant (p = 0.038) but weak (Spearman's Rank Correlation Coefficient = 0.329).

Discussion

Our study is the first to assess the significance of 4C Mortality Score in patients with COVID-19-related AIS. The score was created to predict mortality in hospitalised patients with COVID-19 [10] and further studies suggest that it could be applied to other respiratory system infections [12]. Our study shows that in the specific group of patients with COVID-19-associated AIS, who are in danger of not only death but also lifelong disability, 4C Mortality Score at onset could be a predictor of functional outcome after stroke. What's

more, patients who died of COVID-19-associated AIS had a statistically higher 4C Mortality Score at onset than those who survived.

A case definition of COVID-19-associated stroke was recently proposed [13]. All of the patients included in this study fulfilled both major criteria of this definition i.e. clinical and neuroradiological evidence of acute stroke and SARS-CoV-2 detection by PCR testing. Twelve patients (23%) fulfilled two minor criteria (allowing us to diagnose probable COVID-19-associated stroke) and 29 (56%) fulfilled one minor criterion (allowing us to diagnose possible COVID-19-associated stroke). However, a full assessment of minor criteria was in some cases impossible because the levels of D-dimers and lactate dehydrogenase were not routinely assessed in some hospitals and information concerning mild infection symptoms preceding the stroke could be missing from the source medical documentation.

Moreover, the minor criteria do not cover those patients who were asymptomatic during onset of the stroke (but tested positive for COVID-19 at admission) or those who tested positive a few days after developing stroke symptoms while being hospitalised (we included those patients in the study if there was no proof of an in-hospital epidemiological outbreak, assuming that the stroke may have occurred during the 'window period' for COVID-19) [14]. We combined AIS patients with symptomatic and asymptomatic SARS-CoV-2 infection patients in a unified study group to reflect the real-life clinical diversity of COVID-19-associated AIS.

Our study has some important limitations. Firstly, it was of retrospective character and our observations need to be confirmed by prospective studies in larger cohorts of patients. Secondly, we did not analyse the impact of other factors (such as the type of reperfusion therapy received or the physical rehabilitation of the patient). Thirdly, the assessment of Glasgow Coma Scale (GCS) may be flawed in patients with aphasia, thus modifying the result of 4C Mortality Score. However, as the Score does not require a specific result of GCS, but only information if the score was 15 points or less, in patients with aphasia we assessed only the quantitative disturbances of consciousness, whereas in patients without aphasia we could fully assess the GCS score. Fourthly, in some cases it is possible that some of the 4C Mortality Score components (such as low GCS score) were positive due to stroke, rather than due to the infection itself, thus impacting upon our results.

Clinical implications/future directions

4C Mortality Score predicts functional outcome at discharge in COVID-19-associated AIS patients, making it potentially a promising prognostic tool. However, further prospective studies are needed to confirm our observations.

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Conflict of interest: *None*

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