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Neurological complications of COVID-19 with particular reference to acute ischaemic stroke

Neurologiczne powikłania COVID-19 ze szczególnym uwzględnieniem ostrego udaru niedokrwiennego mózgu

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Streszczenie

Drugi koronawirus ciężkiego ostrego zespołu oddechowego (SARS-CoV-2) ma udowodnione działanie neurotropowe i wywołuje szereg powikłań neurologicznych. Do szczególnie istotnych komplikacji COVID-19 należą choroby naczyń mózgowych, z których najczęstszy jest ostry udar niedokrwienny mózgu. Niniejsza praca doktorska stanowi cykl trzech prac poświęconych wybranym aspektom neurologicznych powikłań infekcji COVID-19, ze szczególnym uwzględnieniem ostrego udaru niedokrwiennego mózgu.

Celem pierwszej z prac był opis spektrum objawów neurologicznych występujących podczas pierwszych 14 dni hospitalizacji u pacjentów z COVID-19 oraz ocena związku ich występowania ze śmiertelnością wewnątrzszpitalną. Do badania włączono 200 pełnoletnich pacjentów z rozpoznanym COVID-19, niewymagających wentylacji mechanicznej przy przyjęciu, hospitalizowanych w czterech oddziałach klinicznych Szpitala Uniwersyteckiego w Krakowie od marca do września 2020 r. Stu sześćdziesięciu czterech pacjentów prospektywnie wypełniło kwestionariusze dotyczące występowania objawów neurologicznych w trakcie hospitalizacji, a u 36 chorych takie kwestionariusze wypełniono retrospektywnie w oparciu o szczegółową dokumentację medyczną z Oddziału Neurologii. Obecność objawów neurologicznych wykazano u większości chorych (84.5%), przy czym u 10% pacjentów stanowiły one pierwszą manifestację choroby. Najczęściej stwierdzanym objawem było zmęczenie (62.5%). Pacjenci, którzy zmarli podczas hospitalizacji w porównaniu z pacjentami, którzy przeżyli, cechowali się istotnie starszym wiekiem (79 [70.5 – 88.5) vs 63.5 [51 – 77] lat, $p = 0.001$), istotnie częściej występowały u nich ilościowe zaburzenia świadomości (50% vs 9.3%, $p < 0.001$), majaczenie (33.3% vs 4.4%, $p < 0.001$), niedociśnienie tętnicze (50% vs 19.6%, $p = 0.005$) oraz udar mózgu podczas hospitalizacji (18.8% vs 3.3%, $p = 0.026$) lub w wywiadzie (50% vs 7.1%, $p = 0.003$). Pacjenci, którzy przeżyli w porównaniu z chorymi, którzy zmarli, cechowali się istotnie częstszym występowaniem bólu głowy (42.1% vs 0%, $p = 0.012$) i obniżenia nastroju (51.7% vs 0%, $p = 0.003$).

Celem drugiej z prac było określenie, czy skala 4C Mortality Score, stworzona pierwotnie w celu oceny rokowania u hospitalizowanych pacjentów z COVID-19 i jak dotąd badana jedynie w chorobach układu oddechowego, znajduje zastosowanie do oceny rokowania także u pacjentów z ostrym udarem niedokrwiennym mózgu w przebiegu COVID-19. Do badania włączono 52 pacjentów z ostrym udarem niedokrwiennym mózgu w przebiegu COVID-19, hospitalizowanych w siedmiu oddziałach neurologicznych na terenie

województwa małopolskiego pomiędzy sierpniem a grudniem 2020 r. U pacjentów retrospektywnie dokonano oceny w skali 4C Mortality Score w pierwszej dobie udaru oraz zebrano dane dotyczące śmiertelności wewnątrzszpitalnej, stanu neurologicznego przy wypisie (ocenionego za pomocą skali National Institute od Health Stroke Scale, NIHSS) oraz stanu funkcjonalnego przy wypisie (ocenionego za pomocą zmodyfikowanej skali Rankina, mRS). Stwierdzono obecność istotnej statystycznie umiarkowanej korelacji pomiędzy wynikiem w skali 4C Mortality Score w pierwszej dobie udaru a stanem funkcjonalnym chorych przy wypisie ocenionym za pomocą mRS (r_S = 0.565, $p < 0.01$). Pacjenci, którzy zmarli w szpitalu w porównaniu z pacjentami, którzy przeżyli do wypisu, cechowali się istotnie większą punktacją w skali 4C Mortality Score w pierwszej dobie udaru (13.08 +/- 2.71 vs 9.85 ± 3.47, p = 0.04).

Celem trzeciej pracy była ocena profilu klinicznego i rokowania krótkoterminowego u pacjentów z ostrym udarem niedokrwiennym w przebiegu COVID-19 leczonych trombektomią mechaniczną (TM) w Centrum Interwencyjnego Leczenia Udaru Mózgu (CILUM) Szpitala Uniwersyteckiego w Krakowie oraz porównanie ich z grupą pacjentów z ostrym udarem niedokrwiennym bez współistniejącej infekcji SARS-CoV2, leczonych trombektomią mechaniczną w tym samym ośrodku. Do badania włączono 15 pacjentów z ostrym udarem niedokrwiennym mózgu w przebiegu COVID-19 leczonych TM, których porównano ze 167 pacjentami z udarem mózgu leczonymi TM bez współistniejącego zakażenia wirusem SARS-CoV-2. Między grupami nie stwierdzono istotnych statystycznie różnic dotyczących płci, wieku, profilu sercowo-naczyniowych czynników ryzyka, objętości ogniska udarowego opisywanego w badaniu perfuzji TK, odsetka pacjentów leczonych trombolitycznie, odsetka skutecznych reperfuzji (definiowanych jako wynik w skali Thrombolysis in cerebral infarction, TICI, 2b-3) ani rokowania krótkoterminowego (śmiertelność wewnątrzszpitalna, deficyt neurologiczny przy wypisie oceniony w skali NIHSS, stan funkcjonalny przy wypisie oceniony w skali mRS). U pacjentów ze współistniejącą infekcją COVID-19 istotnie dłuższy był czas od przyjazdu do CILUM do rozpoczęcia trombektomii mechanicznej (104.27 [SD=51.47] vs 97.63 [SD = 156.94] minut, p = 0.044) oraz czas trwania hospitalizacji (23.7 [SD = 11.9] vs 10.5 [SD = 6.9] dni, $p < 0.001$).

Podsumowując, wyniki prac wchodzących w skład niniejszej rozprawy doktorskiej wskazują, że objawy neurologiczne występują u większości pacjentów hospitalizowanych z powodu COVID-19. Ponadto, zakażenie wirusem SARS-CoV-2 nie wydaje się pogarszać rokowania u pacjentów z udarem niedokrwiennym mózgu leczonym mechaniczną

trombektomią. Do oceny krótkoterminowego rokowania u pacjentów z udarem niedokrwiennym mózgu ze współistniejącą infekcją COVID-19 przydatna może być skala 4C Mortality Score.

Summary

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) has a proven neurotropic potential and causes variety of neurological complications. Particularly important are cerebrovascular diseases, of which the most common is acute ischaemic stroke. This thesis is a series of three articles dedicated to selected aspects of neurological complications of SARS-CoV2 infection, with particular reference to acute ischaemic stroke.

The aim of the first study was to assess the spectrum of neurological signs and symptoms presented in hospitalised patients with Coronavirus Disease 2019 (COVID-19) within the first 14 days of hospitalisation and to evaluate the association of their presence with in-hospital mortality. 200 adult patients, not requiring mechanical ventilation at admission, hospitalised in four departments of the University Hospital in Kraków between March and September 2020 were included into the study. Questionnaires concerning the presence of neurological signs and symptoms during hospitalisation were performed prospectively in 164 and retrospectively (based on detailed medical documentation) in 36 patients. Neurological signs and symptoms were found in most of the patients (84,5%). In 10% patients they were the first manifestation od COVID-19. The most common symptom was fatigue (62,5%). Patients who died during hospitalisation, compared to patients who survived, were significantly older (79 [70.5 – 88.5) vs 63.5 [51 – 77] years, $p = 0.001$), and more commonly presented decreased level of consciousness (50% vs 9.3%, $p < 0.001$), delirium (33.3% vs 4.4%, $p < 0.001$), arterial hypotension (50% vs 19.6%, $p = 0.005$), stroke during hospitalisation (18.8% vs 3.3%, $p = 0.026$) or had stroke in their medical history (50% vs 7.1%, $p = 0.003$). The patients who survived, compared to the patients who died, more commonly reported headache (42.1% vs 0%, $p = 0.012$) or lowered mood (51.7% vs 0%, $p = 0.003$).

The aim of the second study was to assess if 4C Mortality Score (a scale created to predict mortality in hospitalised COVID-19 patients and so far only evaluated in patients with respiratory disease) can be used to predict outcome of patients with COVID-19-associated acute ischaemic stroke. 52 patients with acute ischaemic stroke associated with COVID-19 infection, hospitalised in seven neurological wards of the Małopolska Voivodship

between August and December 2020 were included into the study. 4C Mortality Score at stroke onset was calculated retrospectively and data on in-hospital mortality, neurological deficit at discharge (measured using National Institute of Health Stroke Scale, NIHSS) and functional deficit at discharge (measured using modified Rankin scale, mRS) was gathered. There was a statistically significant moderate correlation between the 4C Mortality Score at stroke onset and functional outcome at discharge measured using mRS (r_s = 0.565, $p < 0.01$). The patients who died in the hospital compared to those, who survived, had significantly higher 4C Mortality Score at stroke onset (13.08 +/- 2.71 vs 9.85 +/- 3.47, $p = 0.04$).

The aim of the third study was to evaluate clinical profile and short-term outcome of patients with COVID-19 associated acute ischaemic stroke treated with mechanical thrombectomy (MT) in the Comprehensive Stroke Centre (CSC) of the University Hospital in Kraków and to compare them to patients with acute ischaemic stroke treated with MT in the same centre without concomitant SARS-CoV2 infection. The study included 15 patients with COVID-19-associated acute ischaemic stroke treated with MT and 167 patients with acute ischaemic stroke treated with MT without COVID-19. There were no statistically significant differences between the groups concerning sex, age, cardiovascular risk factors profile, stroke volume (as assessed with perfusion CT scanning), the percentage of patients treated with intravenous thrombolysis, the percentage of successful reperfusions (defined as Thrombolysis in cerebral infarction scale, TICI, 2b-3) nor short-term outcome (in-hospital mortality, neurological deficit at discharge measured with NIHSS, functional outcome at discharge measured with mRS). Patients with concomitant COVID-19 infection had significantly longer time from arrival to CSC to groin puncture (104.27 [SD=51.47] vs 97.63 [SD = 156.94] minutes, $p = 0.044$) as well as hospitalisation duration (23.7 [SD = 11.9] vs 10.5 [SD = 6.9] days, $p < 0.001$).

To summarize, the results of studies included in this thesis suggest that neurological symptoms are present in the majority of hospitalised patients with COVID-19. Moreover, SARS-CoV-2 infection does not seem to worsen the outcome of patients with acute ischaemic stroke treated with mechanical thrombectomy. 4C Mortality Score may be useful for assessing short-term outcome of patients with COVID-19-associated acute ischaemic stroke.

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Neurological symptoms in hospitalised patients with COVID-19 and their association with in-hospital mortality

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Introduction

Poland is among the eight worst-hit countries in Europe in terms of the prevalence of novel coronavirus causing Coronavirus Disease 2019 (COVID-19), with more than two and a half million affected people, and nearly 60,000 deaths, as of 11 April, 2021 [1].

Numerous infectious diseases with pandemic and epidemic potential can cause neurological symptoms in their course [2]. With an increasing number of patients, neurological manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection also became apparent, with the first study from Wuhan showing that this could apply to one in every three cases [3]. Later studies revealed that the frequency of neurological symptoms might be even higher, ranging from 57.4% in hospitalised patients with COVID-19 in Spain [4] to 73.0% in a mixed cohort of outpatient and hospitalised patients in a single centre in the state of Washington, USA [5]. However, most of these studies had

a retrospective design which consequently might result in underestimation of the frequency of neurological manifestations in SARS-Cov-2 infection.

Recently, two prospective studies on neurological symptoms in COVID-19 patients were performed, in which neurological consultation was used to identify neurological manifestations [6, 7]. Fleischer et al. showed that nearly 60% of 102 patients infected with the SARS-Cov-2 virus had non-specific neurological involvement with general weakness, cognitive decline or delirium [6]. In another study, the most common neurological complaints in a cohort of 873 Iranian patients were: smell and taste dysfunction, myalgia, headache, and dizziness [7].

Therefore, due to discrepancy in the frequency of neurological symptoms among patients infected with the SARS-Cov-2 virus, we aimed to evaluate the frequency and spectrum of neurological symptoms in COVID-19 patients during the first 14 days of hospitalisation, and to seek any possible association with in-hospital mortality.

Material and methods

We recruited patients admitted between March and September 2020 to four different departments of the University Hospital in Krakow — Neurology, Metabolic Diseases and Diabetology, Internal Medicine, and Otorhinolaryngology — which during the pandemic was transformed into the main centre for patients with the SARS-Cov-2 infection in the region of Lesser Poland. All patients had the diagnosis of COVID-19 confirmed by the detection of SARS-Cov-2 RNA by real-time reverse transcription-polymerase chain reaction (RT-PCR) from a nasopharyngeal swab.

Causes of hospital admission, and therefore inclusion criteria for participation in the study, were as follows: dyspnoea, low blood saturation (≤ 92%), chronic disease which had to be treated in hospital, or lack of possibility of isolation. Excluded were: patients younger than 18 years and those who needed mechanical ventilation on hospital admission.

In most patients (n = 164), a detailed questionnaire concerning the presence of 12 neurological symptoms (headache, dizziness, decreased mood, memory or concentration difficulties, fatigue, visual disturbances, anosmia, ageusia, muscle weakness, myalgia, paraesthesia, and increased sweating) and eight neurological signs (decreased level of consciousness, delirium, ataxia, seizure, stroke/TIA, autonomic disturbances such as diarrhoea, and arterial hypotension < 90/60mmHg or tachycardia > 100/min)

was performed prospectively within 14 days of hospitalisation by both patients and physicians. In the remaining 36 patients, such questionnaires were completed retrospectively on the basis of detailed daily clinical records in the computerised hospital system in the Department of Neurology. We additionally collected data concerning respiratory and gastrointestinal symptoms of COVID-19, comorbidities, and in-hospital mortality.

Written or verbal — in the presence of two witnesses — informed medical consent was obtained from each patient followed prospectively. 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).

We presented categorical data as counts and percentages and continuous data as mean and standard deviation (SD), median and interquartile range (IQR). We tested continuous variables for normality with the Shapiro-Wilk test and compared, as appropriate, by the Student's t-test or by the Mann-Whitney U test. A p-value of 0.05 (two-sided) was considered statistically significant. We performed all statistical analyses with STATISTICA version 13 (Statsoft Inc, Tulsa, OK, USA).

The data confirming the results of this study is available from the corresponding author upon reasonable request.

Results

This study included 200 consecutive patients hospitalised in four departments of the University Hospital in Krakow – Neurology (29.0%, n = 58), Metabolic Diseases and Diabetology (54.5%, n = 109), Internal Medicine (10%, n = 20), and Otorhinolaryngology (6.5%, n = 13). Patients were admitted from home (62.5%, n = 125), another hospital (27.5%, n = 55), nursing home (9.0%, n = 18), or institutional isolation (1.0%, n = 2).

Median patient age during hospitalisation was 65.0 (interquartile range, IQR 52.0-78.5) years and there were 56.0% females (n = 112). Median time from first COVID-19 symptoms to hospital admission was 5 (IQR 3-7) days, whereas the median time from first positive nasopharyngeal swab test to the onset of hospitalisation was 1 (IQR 1-3) day. In 128 patients (64.0%), the following comorbidities were noted: hypertension (57.5%, n = 115), diabetes mellitus (26.5%, n = 53), ischaemic heart disease (17.5%, n = 35), obesity (16.5%, n = 33), chronic renal disease (4.5%, n = 9), cancer (4.5%, n = 9), and chronic obstructive

pulmonary disease or asthma (4.0%, n = 8). Eleven (5.5%) and 19 (14.5%) patients had a history of cancer or stroke, respectively. There were six (3.0%) current and 29 (14.5%) past smokers.

First manifestations of SARS-Cov-2 infection were as follows: cough (57.5%, n = 115), fever (body temperature ≥ 38ºC; 52.0%, n = 104), dyspnoea (48.5%, n = 97), loss of appetite (27.5%, n = 55), diarrhoea (24.0%, n = 48), abdominal pain (18.5%, n = 37) and sore throat (12.5%, n = 25). At day 14 since the onset of hospitalisation, 22 (11%) patients were receiving oxygen therapy and seven (3.5%) were being mechanically ventilated. There were 16 (8.0%) deaths at a median 12.5 (IQR 8.5-28.5) days of hospitalisation.

During a median 14 (IQR 8-22) days of hospitalisation, 169 patients (84.5%) experienced some form of neurological symptom or sign. In 20 patients (10.0%) neurological symptoms were the first manifestation of SARS-Cov-2 infection accompanying respiratory or gastrointestinal symptoms. The most common neurological symptoms were: fatigue (62.5%), decreased mood (45.5%), myalgia (43.5%), muscle weakness (42.5%) and headache (37.0%) (Tab. 1). Most neurological symptoms had an onset within the first three days of hospitalisation, whereas paraesthesia or arterial hypotension < 90/60mmHg occurred later in the disease course (median 6 days, IQR 1-11 or 7.5 days, IQR 3-13, respectively; Tab. 1).

Patients who died during hospitalisation compared to the remainder were older, and more often had a decreased level of consciousness, delirium, arterial hypotension or stroke during or before hospitalisation, whereas those who survived more often suffered from headache or decreased mood (Tab. 2).

When the analysis was restricted to patients followed prospectively, those who died during hospitalisation compared to survivors were older (83 [76–87] vs. 63 [50–77] years, $p < 0.001$) and more often had a decreased level of consciousness (44.4% vs. 7.8%, $p = 0.006$), delirium (50.0% vs. 3.9%, $p < 0.001$), or a history of stroke (44.4% vs. 5.8%, $p = 0.002$) (Tab. 3). Among patients recruited prospectively those who survived compared to the remainder more often complained of decreased mood (54.7% vs. 0.0%, $p = 0.021$) (Tab. 3).

Table 1: Neurological symptoms and signs in patients with COVID-19 during the first 14 days of hospitalisation

Neurological symptom or sign	Presence of neurological symptom or sign	Number of patients n (%)	Onset of neurological symptom or sign (days of hospitalisation, median and IQR)	Duration of neurological symptom or sign (days of hospitalisation, median and IQR)	Number of patients who declared to have neurological symptom or sign before hospitalisation, n (%)
Neurological symptoms					
Headache	No Yes Not possible to assess	111 (55.5) 74 (37.0) 15 (7.5)	2 (1–5)	2 (1–3)	11 (5.5)
Dizziness	No Yes Not possible to assess	136 (68.0) 63 (31.5) 1 (0.5)	3 (1–7)	2 (1–2)	8 (4.0)
Decreased mood	No Yes Not possible to assess	94 (47.0) 91 (45.5) 15 (7.5)	2 (1–8)	4 (2–8)	2 (1.0)
Memory or concentration difficulties	No Yes Not possible to assess	152 (76.0) 34 (17.0) 14 (7.0)	1 (1–8)	3 (2–5)	4 (2.0)
Fatigue	No Yes Not possible to assess	60 (30.0) 125 (62.5) 15 (7.5)	1 (1–4)	5 (2–8)	10 (5.0)
Visual disturbances	No Yes Not possible to assess	174 (87.0) 11 (5.5) 15 (7.5)	1 (1–10)	2 (1–3)	1 (0.5)
Anosmia	No Yes Not possible to assess	142 (71.0) 43 (21.5) 15 (7.5)	1 (1–1)	4 (2–9)	7 (3.5)
Ageusia	No Yes Not possible to assess	131 (65.5) 54 (27.0) 15 (7.5)	1 (1–4)	4 (2–8)	5 (2.5)
Muscle weakness	No Yes Not possible to assess	102 (51.0) 85 (42.5) 13 (6.5)	1 (1–6)	4 (1–8.5)	17 (8.5)
Myalgia	No Yes Not possible to assess	112 (56.0) 87 (43.5) 1 (0.5)	1 (1–6)	2 (1–5)	10 (5.0)
Paresthesia	No Yes Not possible to assess	139 (69.5) 46 (23.0) 15 (7.5)	6 (1–11)	1 (1–4)	3 (1.5)
Increased sweating	No Yes Not possible to assess	116 (58.0) 71 (35.5) 13 (6.5)	3 (1–8)	2 (1–6)	7 (3.5)
Neurological signs					
Decreased level of consciousness	No Yes Not possible to assess	174 (87.0) 25 (12.5) 1 (0.5)	1 (1–4)	5 (3–15)	1 (0.5)
Delirium	No Yes Not possible to assess	184 (92.0) 15 (7.5) 1 (0.5)	3 (1–7)	7 (4–9)	3 (1.5)
Diarrhoea	No Yes Not possible to assess	137 (68.5) 62 (31.0) 1 (0.5)	3 (1–6)	2 (1–3)	8 (4.0)
Arterial hypotension < 90/60 mmHg	No Yes Not possible to assess	156 (78.0) 44 (22.0) 0 (0.0)	7.5 (3–13)	1 (1–2)	0 (0.0)
Tachycardia > 100/min	No Yes Not possible to assess	144 (72) 56 (28) 0 (0.0)	3.5 (1–9)	2 (1–3)	0 (0.0)
Ataxia	No Yes Not possible to assess	188 (94.0) 11 (5.5) 1 (0.5)	1.5 (1–8)	1 (1–1)	1 (0.5)
Seizure	No Yes Not possible to assess	198 (99.0) 1 (0.5) 1 (0.5)	1 (1–1)	0.5 (0–1)	0 (0.0)
Stroke or TIA	No Yes Not possible to assess	188 (94.0) 5 (2.5) 7 (3.5)	5 (1–11)	1 (1–1)	0 (0.0)

Table 2: Comparison of patients with COVID-19 who survived or died during hospitalisation

	Patients who survived during hospitalisation n = 184	Patients who died during hospitalisation n = 16	P-value
Demographics			
Female sex	103 (55.6)	9 (56.2)	0.982
Age	63.5 (51–77)	79 (70.5–88.5)	0.001
First COVID-19 symptoms			
Fever	94 (51.2)	10 (62.5)	0.381
Cough	107 (58.2)	8 (50.0)	0.527
Sore throat	23 (12.5)	2 (12.5)	1.000
Loss of appetite	52 (28.3)	3 (18.8)	0.413
Dyspnoea	88 (47.8)	10 (62.5)	0.260
Diarrhoea	44 (23.9)	4 (25.0)	0.922
Abdominal pain	35 (19.0)	2 (12.5)	0.519
Neurological symptoms and signs			
Headache	74 (42.1)	0 (0.0)	0.012
Dizziness	49 (27.8)	0 (0.0)	0.065
Decreased mood	91 (51.7)	0 (0.0)	0.003
Memory or concentration difficulties	31 (17.6)	3 (30.0)	0.324
Fatigue	122 (69.3)	3 (33.3)	0.060
Visual disturbances	11 (6.3)	0 (0.0)	0.439
Decreased level of consciousness	17 (9.3)	8 (50.0)	< 0.001
Delirium	8 (4.4)	5 (33.3)	< 0.001
Seizure	0 (0.0)	1 (6.2)	0.080
Ataxia	4 (2.2)	0 (0.0)	1.000
Stroke/TIA	6 (3.3)	3 (18.8)	0.026
Anosmia	42 (23.9)	1 (11.1)	0.687
Ageusia	53 (30.1)	1 (11.1)	0.287
Muscle weakness	80 (44.9)	5 (55.6)	0.532
Myalgia	69 (39.2)	4 (44.4)	0.741
Paresthesia	44 (35.0)	2 (22.2)	1.000
Diarrhoea	59 (32.1)	3 (20.0)	0.400
Increased sweating	68 (38.6)	3 (27.3)	0.538
Arterial hypotension (< 90/60mmHg)	36 (19.6)	8 (50.0)	0.005
Tachycardia (> 100/min)	50 (27.2)	6 (37.5)	0.378
Any neurological symptom or sign	158 (85.9)	11 (68.8)	0.069
Comorbidities			
Hypertension	106 (62.4)	9 (64.3)	0.885
Ischaemic heart disease	31 (18.3)	4 (28.9)	0.312
Diabetes mellitus	47 (27.8)	6 (42.9)	0.233
History of stroke	12 (7.1)	7 (50.0)	< 0.001
Asthma/Chronic Obstructive Pulmonary Disease	8 (4.7)	0 (0.0)	1.000
Cancer	19 (11.2)	1 (7.1)	1.000
— No cancer — Current cancer — History of cancer	150 (88.8) 8 (4.7) 11 (6.5)	13 (92.9) 1 (7.1) 0 (0.0)	0.580
Chronic renal disease	7 (4.1)	2 (14.3)	0.143
Obesity	30 (17.8)	3 (21.4)	0.720
Smoking	33 (19.9)	2 (14.3)	1.000
— No smoking — Current smoking — History of smoking	133 (80.1) 5 (3.0) 28 (16.9)	12 (85.7) 1 (7.1) 1 (7.1)	0.479

Table 3: Comparison of patients with COVID-19 recruited prospectively who survived or died during hospitalisation

	Patients who survived during hospitalisation n = 155	Patients who died during hospitalisation n = 9	P-value
Demographics			
Female sex	94 (60.7)	4 (4.4)	0.485
Age	63 (50–77)	83 (76–87)	< 0.001
First COVID-19 symptoms			
Fever	77 (49.7)	4 (44.4)	1.000
Cough	88 (56.8)	2 (22.2)	0.080
Sore throat	118 (11.6)	1 (11.1)	1.000
Loss of appetite	44 (28.4)	2 (22.2)	1.000
Dyspnoea	67 (43.2)	6 (66.7)	0.169
Diarrhoea	37 (23.9)	0 (0.0)	0.211
Abdominal pain	29 (18.7)	0 (0.0)	0.363
Neurological symptoms and signs			
Headache	65 (43.9)	0 (0.0)	0.073
Dizziness	43 (29.1)	0 (0.0)	0.322
Decreased mood	81 (54.7)	0 (0.0)	0.021
Memory or concentration difficulties	26 (17.6)	3 (50.0)	0.081
Fatigue	110 (74.30	2 (40.0)	0.112
Visual disturbances	11 (7.4)	0 (0.0)	1.000
Decreased level of consciousness	12 (7.8)	4 (44.4)	0.006
Delirium	6 (3.9)	4 (50.0)	< 0.001
Seizure	0 (0.0)	0 (0.0)	1.000
Ataxia	1 (0.7)	0 (0.0)	1.000
Stroke/TIA	4 (2.6)	1 (11.1)	0.248
Anosmia	39 (26.4)	1 (20.0)	1.000
Ageusia	52 (35.1)	1 (20.0)	0.659
Muscle weakness	68 (45.3)	2 (40.0)	1.000
Myalgia	59 (39.9)	2 (40.0)	1.000
Paresthesia	27 (25.0)	1 (20.0)	1.000
Diarrhoea	52 (33.6)	0 (0.0)	0.057
Increased sweating	65 (43.9)	2 (40.0)	1.000
Arterial hypotension (< 90/60mmHg)	35 (22.6)	4 (44.4)	0.218
Tachycardia (> 100/min)	45 (29.1)	3 (33.3)	0.721
Any neurological symptom or sign	135 (87.1)	6 (66.7)	0.115
Comorbidities			
Hypertension	95 (61.3)	7 (77.8)	0.321
Ischaemic heart disease	27 (17.4)	3 (33.3)	0.213
Diabetes mellitus	43 (27.7)	3 (3.3)	0.711
History of stroke	9 (5.8)	4 (44.4)	0.002
Asthma/Chronic Obstructive Pulmonary Disease	8 (5.2)	0 (0.0)	1.000
Cancer	19 (11.2)	1 (7.1)	1.000
— No cancer — Current cancer — History of cancer	139 (89.7) 5 (93.3) 11 (7.1)	8 (88.9) 1 (11.1) 0 (0.0)	0.332
Chronic renal disease	7 (4.5)	2 (22.2)	0.079
Obesity	29 (18.7)	1 (11.1)	1.000
Smoking	28 (18.4)	2 (22.2)	0.675
— No smoking — Current smoking — History of smoking	124 (81.6) 4 (2.6) 24 (15.8)	7 (77.8) 1 (11.1) 1 (11.1)	0.504

Discussion

Our study showed that different neurological symptoms exerted a diverse association with in-hospital mortality in patients with COVID-19. Some of them, possible to assess regardless of patient cooperation such as delirium or decreased level of consciousness, were linked to the risk of death during hospitalisation. This observation was in line with a previous study in which a short and simple scale for mortality risk was validated in a cohort of more than 20,000 patients with COVID-19 and which consisted of eight parameters with a level of consciousness among others [8]. A recent Italian study also confirmed that patients with COVID-19 and delirium on admission had a nearly two-fold higher risk of in-hospital mortality compared to those without delirium [9].

In another study, consisting of a retrospective analysis of electronic medical records of 307 COVID-19 patients in Turkey, it was shown that altered mental status was the most common neurological manifestation and associated with a higher mortality rate [10]. On the other hand, in our study some symptoms which could be evaluated only in those patients who were able to fill out the questionnaire, such as headache or decreased mood, increased the chance of survival. Our results were similar to the findings of a prospective study of nearly 900 patients with SARS-Cov-2 infection where the presence of headache was a protective factor against death due to COVID-19 [7]. The frequency of headache in previous studies has been reported as between 7% and 75%, with higher percentages in European populations than in Chinese cohorts [11].

We hypothesise that the protective role of headache and decreased mood in terms of mortality due to COVID-19 could be — at least partially — explained by the inflammatory process occurring in the body of these patients and leading to virus elimination [12]. Indeed, in a recent Chinese study of 77 patients with COVID-19, those who suffered from anxiety had higher serum levels of IL-6 and IL-10, whereas those with depression had higher CD8+ T-cell count and lower CD4+/CD8+ ratio compared to the remainder [13]. What's more, as was shown in a large American cohort of nearly 4,000 patients with prior SARS-CoV-2 infection, the severity of COVID-19 symptoms and the presence of headache increase the risk of subsequent major depression by 2.6 and 1.3-fold, respectively [14]. Recently, so-called lesser neurological symptoms such as fatigue, inability to concentrate, myalgia, and headache, were found to have the potential to become chronic and result in the syndrome recently labelled as Long Covid [15].

We also revealed that patients with COVID-19 with previous stroke and older age had a greater risk of in-hospital mortality. Stroke during COVID-19 was also associated with increased in-hospital mortality in the whole group but not in the prospective cohort, probably due to severe neurological deficit which prevented these patients from filling out the questionnaire. Previous research has shown that chronic neurological comorbidity increases the risk of in-hospital mortality [16, 17]. A recent meta-analysis of 18 studies, mostly of retrospective design, revealed that the mortality rate in COVID-19 patients with concomitant stroke was concerning and, especially in relation to ischaemic stroke, higher than would be expected due to stroke itself [18].

Several possible aetiologies of stroke in COVID-19 patients include hypercoagulable state, cardioembolism, and direct viral-induced pathology of the endothelium, whereas increased mortality rate of stroke patients could be, at least partly, explained by limited hospital resources [19]. A previous meta-analysis of 109 articles showed that the risk of mortality was higher in older patients, which was similar to the results of our study, but additionally pointed to male gender, dyspnoea, diabetes mellitus, and hypertension as risk factors for death [20]. We were unable to replicate these findings, probably due to the small number of patients who died during our study.

Our study showed that neurological symptoms were found in 84.5% of patients hospitalised due to COVID-19. This proportion was quite high compared to the previous retrospective studies from Wuhan [3] and Washington state [5]. However, in contrast to previous research, 82% of our patients were followed-up prospectively during hospitalisation with a detailed clinical questionnaire.

Therefore, physicians should proactively ask patients with COVID-19 about neurological symptoms in the course of hospitalisation. Additionally, most neurological symptoms occurred at the beginning of hospitalisation which was similar to the experience of Chinese authors [21].

The most common neurological symptoms in our cohort were fatigue, decreased mood, myalgia, muscle weakness and headache. A recent review of the literature showed that the majority of COVID-19 patients complained of non-specific neurological manifestations early in the disease course, with headache, dizziness, excessive tiredness, myalgia, anosmia/ hyposmia, and ageusia/dysgeusia being the most common [22]. Even in a detailed study of 53 patients encompassing data of cerebrospinal fluid and radiological analysis together with electroencephalography, the most common neurological features of hospitalised COVID-19 patients, apart from abnormalities in neurological examination, were cognitive impairment,

hyposmia, headache, general muscle weakness and pain [23]. These symptoms usually occurred during the acute phase of COVID-19 infection, following an incubation period of 5-6 days, but some of them, especially fatigue and cognitive impairment, became chronic during the post-infectious phase [22].

Mechanisms leading to neurological symptoms in COVID-19 might comprise hypoxia and hypercoagulability [12]. Moreover, the SARS-Cov-2 virus exerts its neurotrophic effect by interaction with ACE-2 receptor which is found in the brainstem among other body localisations [24, 25]. As shown recently, invasion of hypothalamic circuits by the SARS-Cov-2 virus may be responsible for mediating both central and peripheral nervous system symptoms [26]. The role of hyperactivity of the immune system with the cytokine storm has also been considered [27].

Our study has several important limitations. Firstly, we performed additional tests to evaluate the presence of subjective neurological symptoms only in a minority of patients. Secondly, we did not analyse the significance of paraclinical tests such as bloodwork or chest X-ray, which was beyond the scope of this report. Thirdly, due to severe neurological state, in some patients it was impossible to assess the presence of subjective neurological symptoms such as headache or decreased mood. Fourthly, there was a risk of selection bias due to the small sample of patients recruited in the Departments of Internal Medicine and Otorhinolaryngology. And fifthly, the small number of patients who died during hospitalisation did not allow for multivariate analysis.

Conclusions

Our study demonstrates that neurological symptoms occur in most hospitalised patients with COVID-19 and that some of them, such as a decreased level of consciousness and delirium, increase the risk of in-hospital mortality. Future studies on larger patient populations are needed to evaluate how the presence of these neurological manifestations could be incorporated into prognostic scales for patients with COVID-19.

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

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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 the 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 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.

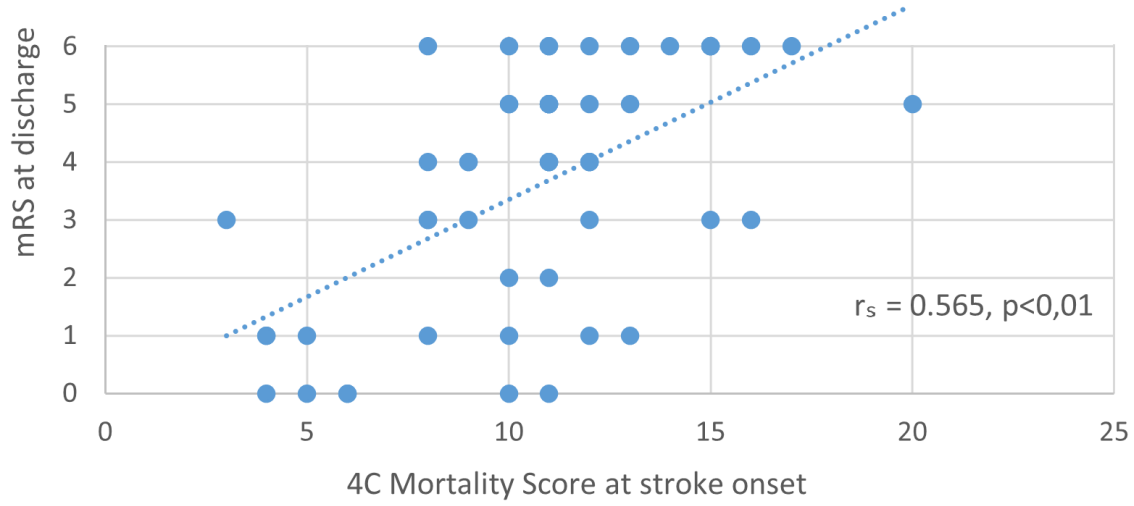
A concomitant infection requiring antibiotic use was present in 30 (58%) patients: pneumonia in 17 patients (33%), both pneumonia and urinary tract infection in four (8%), and nine patients (17%) received antibiotics due to infection of unknown source. Seven (13%) patients were diagnosed with viral pneumonia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

Table 1 – The frequency of cardiovascular risk factors and stroke-associated infections requiring antibiotic therapy in patients with COVID-19-associated acute ischemic stroke

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%)

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).

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



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 is 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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Mechanical thrombectomy in COVID-19-associated ischaemic stroke: patient characteristics and outcomes in a single-centre study

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Introduction

The majority of hospitalised patients with SARS-CoV2 experience neurological symptoms of varying severity [1]. COVID-19 is proven to be a risk factor for acute ischaemic stroke (AIS) [2]. AIS in patients with a SARS-CoV2 infection is associated with a more severe neurological deficit and higher in-hospital mortality [3]. The incidence of AIS in patients with COVID-19 is estimated at around 1.5%, although this percentage is higher among critically ill patients [4].

Mechanical thrombectomy (MT) is an endovascular method of stroke treatment that has revolutionised the outcomes of patients with emergent large artery occlusion (LAO). Recent studies suggest that AIS in COVID-19 patients is more commonly associated with LAO [5], and that concomitant SARS-CoV2 infection increases mortality in patients with LAO [6]. At the same time, during the COVID-19 pandemic a decline in the global number of stroke hospitalisations and MT procedures has been observed [7].

Clinical rationale for the study

The literature on the outcomes of COVID-19-associated AIS patients treated with MT is scarce, and the studies show divergent results. These have been summarised in a recent systematic review [8]. The characteristics and treatment results of this group of patients still need to be evaluated.

Therefore, the aim of this study was to assess the clinical profiles and outcomes of patients with a confirmed COVID-19 infection and AIS treated with MT at the University Hospital in Krakow, Poland and to compare them to those of AIS patients treated with MT at the same time, but without a concomitant SARS-CoV2 infection.

Materials and methods

In this retrospective study, we analysed the medical documentation of patients who had undergone MT for AIS in the Comprehensive Stroke Centre (CSC) of the University Hospital in Krakow, Poland during the COVID-19 pandemic between March 2020 and May 2021. Included were patients with a COVID-19 infection confirmed by a positive SARS CoV2 PCR or antigen test from a nasopharyngeal swab obtained at admission or in the referring hospital, or before hospitalisation (if the patient did not match the criteria for recovery). The control group consisted of 167 AIS patients treated with MT in the CSC between March 2020 and February 2021, who tested negative for SARS-CoV2 at admission. Excluded were patients who were negative for COVID-19 at admission but who tested positive during hospitalisation, or those who were transferred to another centre and therefore lost to follow-up.

The procedures for acute stroke causative treatment in Małopolska Voivodship, where our centre is located, have been described elsewhere [9]. AIS patients with and without COVID-19 followed the same pathway of care. MT patients without SARS-CoV2 infection were admitted to the Stroke Unit, while those with a confirmed COVID-19 infection were transferred to a specialised Neurology Ward for COVID-19 (+) patients, where they were treated by neurologists from the same centre, with the same level of experience in acute stroke care. The guidelines for treatment of COVID-19 changed during the course of the pandemic, so the patients with SARS CoV2 infection were treated according to the international recommendations pertaining at the time of their hospitalisation.

The patients who qualified for the study were followed according to the standard protocol of the Krakow Stroke Data Bank, as described in previous publications from our centre [10]. For the purposes of this study, we analysed the patients' age, sex, the presence and number of cardiovascular risk factors, time from stroke onset to the arrival at the CSC, time from arrival at the CSC to groin puncture, number of days of hospitalisation, treatment with intravenous thrombolysis, the immediate radiological effect of thrombectomy (measured using Thrombolysis in Cerebral Infarction scale, TICI), the neurological deficit (measured

using National Institute of Health Stroke Scale, NIHSS) at admission and discharge from our centre, the functional outcome (measured using modified Rankin Scale, mRS) at discharge, and in-hospital mortality. Where available, the computed tomography perfusion imaging parameters at admission calculated using RAPID software (a postprocessing tool used for qualification for MT in DAWN and DEFUSE-3 trials) [11, 12] were also analysed. We also analysed the available laboratory test results — fibrinogen, D-dimer, lactate dehydrogenase (LDH), lymphocyte count, and C-reactive protein (CRP).

The results were compared between groups of AIS patients with and without a COVID-19 infection. Statistical analysis was performed using a PS Imago Pro 6.0 program. We presented categorical data as counts and percentages, and continuous data as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical data was compared between groups using a Chi-square test. We tested continuous variables for normality with a Shapiro-Wilk test and compared them between groups using a t-Student test for normally distributed data and, in other cases, using a Mann-Whitney U test. We considered a two-sided p-value of less than 0.05 to be statistically significant.

In patients with COVID-19, we also noted the clinical and radiological symptoms of lung involvement. HRCT (high resolution computed tomography) images were analysed by the artificial intelligence technology software YITU Healthcare to automatically measure the relative (%) volume of inflammation in both lungs (the methodology was as described in a previous work from our centre) [13]. The chest X-ray images were assessed by a radiologist using a semiquantitative chest X-ray severity score [14].

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

Results

We identified 16 patients with a COVID-19 infection and AIS who received treatment with MT in the CSC between March 2020 and May 2021. One patient was transferred after procedure to an Intensive Care Unit of another hospital, lost to follow-up, and not included in the final analysis. Four patients were diagnosed with COVID-19 before the onset of stroke, and two of them had already been hospitalised when the stroke occurred. The patients' individual characteristics, including their SARS-CoV2 infection clinical picture, are set out in Table 1.

Table 1 part 1 - Characteristics of COVID-19-associated MT patients treated with MT in CSC between March 2020 and May 2021

	Age, sex	Comorbidities	Time from stroke onset to arrival (mins)	NIHSS at admission to CSC	LAO localisation	Intravenous thrombolysis (0 = no, 1 = yes)	Perfusion CT parameters (as calculated by RAPID software)	TICI	COVID-19 clinical and radiological symptoms	Treatment of COVID-19	Days of hospitalisation	Complications	Outcome
1	66, M	Arterial hypertension Aortic aneurysm Atrial fibrillation Peripheral atherosclerosis	490	16	M1-LMCA	0	CBF < 30% = 62 mL Tmax > 6 s = 215 mL Mismatch volume = 153 mL	0	Sore throat Fever Cough Desaturation Lung involvement (HRCT) = 14.21%	Passive oxygen therapy dexamethasone LMWH	50	Haemorrhagic transformation Brain oedema Pneumonia Splenic haematoma	NIHSS = 17 mRS = 5
2	79, F	Metastatic breast cancer Arterial hypertension Atrial fibrillation Peripheral atherosclerosis Dyslipidemia	174	15	RICA	0	—	0	— Chest X-ray severity score = 15	LMWH	30	Deep vein thrombosis	NIHSS = 16 mRS = 5
3	56, F	Arterial hypertension Dyslipidemia Beast cancer	518	16	M1-RMCA	1	CBF < 30% = 20 mL Tmax > 6 s = 61 mL Mismatch volume = 41 mL	3	— Lung involvement (HRCT) = 9.24%	LMWH	10	—	NIHSS = 2 mRS = 1
4	49, M	Arterial hypertension Chronic kidney disease Kidney transplant in 2002 GERD Skin melanoma in the past	0	2	LICA	1	—	3	Cough Fever Chest X-ray severity score = 7	LMWH	15	Deep vein thrombosis	NIHSS = 2 mRS = 1
5	82, F	Arterial hypertension History of stroke Hypothyroidism Dementia	102	20	M1-RMCA	1	CBF < 30% = 34 mL Tmax > 6 s = 151 mL Mismatch volume = 117 mL	3	Cough desaturation Chest X-ray severity score = 8	Passive oxygen therapy	2	Haemorrhagic transformation Subarachnoid haemorrhage	Deceased
6	62, M	Arterial hypertension Peripheral atherosclerosis Diabetes mellitus Obesity History of smoking Alcohol abuse Gout	300	15	M1-RMCA	1	—	3	Desaturation Chest X-ray severity score = 4	Passive oxygen therapy Dexamethasone LMWH	28	RICA dissection Pneumonia	NIHSS = 6 mRS = 2
7	83, F	Arterial hypertension Atrial fibrillation Peripheral atherosclerosis Dyslipidemia Diabetes mellitus Obesity	250	21	LMCA + LACA	1	—	3	Desaturation Lung involvement (HRCT) = 1.82%	Passive oxygen therapy LMWH	18	Clostridium difficile infection	NIHSS = 16 mRS = 5
8	85, F	Arterial hypertension Atrial fibrillation Dyslipidemia Peripheral atherosclerosis Dementia	729	21	M1-LMCA	0	CBF < 30% = 7 mL Tmax > 6 s = 95 mL Mismatch volume = 88 mL	3	Desaturation Chest X-ray severity score = 10	Passive oxygen therapy Dexamethasone LMWH	21	Haemorrhagic transformation Pneumonia	NIHSS = 22 mRS = 5

Table 1 part 2 - Characteristics of COVID-19-associated MT patients treated with MT in CSC between March 2020 and May 2021

	Age, sex	Comorbidities	Time from stroke onset to arrival (mins)	NIHSS at admission to CSC	LAO localisation	Intravenous thrombolysis (0 = no, 1 = yes)	Perfusion CT parameters (as calculated by RAPID software)	TICI	COVID-19 clinical and radiological symptoms	Treatment of COVID-19	Days of hospitalisation	Complications	Outcome
9	72, F	Arterial hypertension Atrial fibrillation Dyslipidemia Hypothyroidism Thrombocytopenia	276	4	M2-LMCA	0	CBF < 30% = 0 mL Tmax > 6 s = 16 mL Mismatch volume = 16 mL	3	— Lung involvement (HRCT) = 2.08%	LMWH	18	Haemorrhagic transformation Pneumonia	NIHSS = 4 mRS = 2
	Age, sex	Comorbidities	Time from stroke onset to arrival (mins)	NIHSS at admission	LAO	Intravenous thrombolysis	Perfusion CT parameters	TICI	COVID-19 clinical and radiological symptoms	Treatment of COVID-19	Days of hospitalisation	Complications	Outcome
10	78, M	Arterial hypertension Chronic heart failure Atrial fibrillation Prostate hypertrophy Peripheral atherosclerosis	265	17	M2-LMCA	1	CBF < 30% = 0 mL Tmax > 6 s = 141 mL Mismatch volume = 141 mL	3	Desaturation Lung involvement (HRCT) = 44.12%	Passive oxygen therapy Dexamethasone LMWH	36	Haemorrhagic transformation Pneumonia	NIHSS = 1 mRS = 0
11	70, F	Arterial hypertension Atrial fibrillation Peripheral atherosclerosis Dyslipidemia Diabetes mellitus Double mastectomy (2010)	485	7	V1-RVA	0	CBF < 30% = 0 mL Tmax > 6 s = 8 mL Mismatch volume = 8 mL	3	Desaturation Lung involvement (HRCT) = 19.52%	Passive oxygen therapy Dexamethasone LMWH Remdesivir	21	Humerus fracture	NIHSS = 2 mRS = 2
12	70, M	Arterial hypertension Coronary artery disease Peripheral atherosclerosis History of TIA Dyslipidemia Diabetes mellitus	282	20	LICA	1	CBF < 30% = 22 mL Tmax > 6 s = 59 mL Mismatch volume = 37 mL	3	Desaturation Lung involvement (HRCT) = 49.79%	Passive oxygen therapy Dexamethasone LMWH	30	Pneumonia Clostridium difficile infection	NIHSS = 12 mRS = 5
13	68, M	Arterial hypertension Diabetes mellitus Coronary artery disease Peripheral atherosclerosis Biological heart valve	288	17	M1-LMCA	0	CBF < 30% = 0 mL Tmax > 6 s = 36 mL Mismatch volume = 36 mL	2b	Desaturation Lung involvement (HRCT) = 0.41%	Passive oxygen therapy Dexamethasone LMWH Remdesivir	32	UTI Urinary retention	NIHSS = 6 mRS = 1
14	55, M	Peripheral atherosclerosis History of smoking	296	8	LICA	0	CBF < 30% = 5 mL Tmax > 6s = 85 mL Mismatch volume = 80 mL	3	Dyspnoea Fever Lung involvement (HRCT) = 17.53%	Passive oxygen therapy Dexamethasone LMWH Remdesivir	32	Pneumonia	NIHSS = 2 mRS = 1
15	65, F	Peripheral atherosclerosis Bladder cancer Kidney cancer	154	5	RICA	0	CBF < 30% = 0 mL Tmax > 6 s = 32 mL Mismatch volume = 32 mL	0	— Lung involvement (HRCT) = 2.28%	LMWH	15	RICA dissection	NIHSS = 5 mRS = 2

The patients were aged 49 to 85 with a median age of 70 years (IQR = 17). Eight (53.3%) were female. The most common cardiovascular risk factor was arterial hypertension, found in 13 (86.7%) patients. There were no statistically significant differences between groups of patients with and without COVID-19 with respect to age, sex, the presence of individual cardiovascular risk factors, or the total amount of cardiovascular risk factors (Tab. 2).

Table 2 - Comparison of COVID (+) and COVID (–) patients with AIS treated with M

	COVID (+)	COVID (–)	
Demographics	N = 15*	N = 167*	
Age (years)	70 (IQR = 17)	70 (IQR = 17)	p = 0.965
Female sex (%)	8 (53.3%)	83 (49.7%)	p = 1.000
Cardiovascular risk factors	N = 15*	N = 167*	
Arterial hypertension (%)	13 (86.7%)	115 (68.9%)	p = 0.237
Coronary artery disease (%)	2 (13.3%)	38 (22.8%)	p = 0.528
Artificial heart valve (%)	0 (0%)	4 (2.4%)	p = 1.000
Atrial fibrillation (%)	7 (46.7%)	69 (41.3%)	p = 0.787
Peripheral artery atherosclerosis (%)	11 (73.3%)	129 (77.2%)	p = 0.751
History of stroke/TIA (%)	2 (13.3%)	16 (9.6%)	p = 0.647
Dyslipidemia (%)	7 (46.7%)	56 (33.5%)	p = 0.396
Diabetes mellitus (%)	5 (33.3%)	34 (20.4%)	p = 0.320
Obesity (%)	2 (13.3%)	14 (8.4%)	p = 0.626
History of smoking (%)	2 (13.3%)	39 (23.4%)	p = 0.526
Chronic kidney disease (%)	1 (6.7%)	15 (9%)	p = 1.000
Total sum of risk factors	3.5 (SD = 1.6)	3.2 (SD = 1.5)	p = 0.575
CT perfusion parameters	N = 11	N = 138	
CBF < 30% [mL]	13.6 (SD = 19.8)	21.0 (SD = 32.9)	p = 0.560
Tmax > 6 s [mL]	81.7 (SD = 64.4)	121.1 (SD = 82.6)	p = 0.096
Mismatch volume [mL]	68.1 (SD = 50.8)	100.0 (SD = 71.5)	p = 0.117
Disease course	N = 15*	N = 167*	
Time from stroke onset to admission (min)	307.3 (SD = 183.7)	227.3 (SD = 115.7) N = 166	p = 0.062
Time from admission to groin puncture	104.27 (SD = 51.47)	97.63 (SD = 156.94)	p = 0.044
NIHSS score at admission	13.3 (SD = 6.6)	15.5 (SD = 8)	p = 0.505
Intravenous thrombolysis (%)	7 (46.7%)	105 (62.9%)	p = 0.270
Full reperfusion (TICI 2b-3) (%)	12 (80%)	148 (88.6%)	p = 0.398
NIHSS at discharge	8.1 (SD = 7.1) N = 14	8.8 (SD = 9.6) N = 145	p = 0.778
mRS at discharge	2.9 (SD = 2)	3.1 (SD = 2.1)	p = 0.817
In-hospital mortality (%)	1 (6.7%)	21 (12.6%)	p = 0.699
Days of hospitalisation	23.7 SD = 11.9)	10.5 (SD = 6.9)	p < 0.001
Laboratory tests results			
Fibrinogen [g/L]	4.07 (SD = 1.88) N = 2	2.87 (SD = 1.09) N = 146	Analysis impossible, sample too small
D-dimer [mg/L]	10.1 (SD = 12.36) N = 14	7.46 (SD = 9.56) N = 16	p = 0.580
Ldh [u/L]	330.92 (SD = 158.58) N = 12	224.62 (SD = 55.69) N = 13	p = 0.015
Lymphocyte count [1 x 10^3/uL]	1.09 (SD = 0.50) N = 14	1.60 (SD = 0.64) N = 60	p = 0.003
CRP [mg/L]	39.77 (SD=38.02) N = 15	17.80 (SD = 23.25) N = 162	p = 0.004

*unless specified otherwise

CT perfusion with post-processing analysis with RAPID software was performed in 11 and 138 patients with, and without, COVID-19 infection respectively. There were no statistically significant differences in the volumes of total ischaemia, penumbra or necrosis between patients with and without COVID-19 infection (Tab. 2).

Patients with COVID-19 had a longer time from stroke onset to arrival at the Comprehensive Stroke Centre [307.3 (SD = 183.7) vs. 227.3 (SD = 115.7) minutes], but this difference was not statistically significant ($p = 0.062$). They also had a longer time from arrival at the CSC to groin puncture: this difference was small but statistically significant [104.27 (SD = 51.47) vs. 97.63 (SD = 156.94) minutes, $p = 0.044$] (Tab. 2). There were no statistically significant differences between the compared groups with respect to the severity of neurological deficit at admission and discharge (measured using the NI HSS scale), the functional outcome at discharge (measured using the mRS scale), the percentage of patients treated with intravenous thrombolysis, the percentage of successful reperfusions (defined as TICI 2b-3), or in-hospital mortality. There was a statistically significant difference between the groups concerning the number of days of hospitalisation: 23.7 (SD = 11.9) for COVID (+) patients versus 10.5 (SD = 6.9) for COVID (–) patients, $p < 0.001$.

The levels of CRP and LDH were significantly higher, and the lymphocyte count significantly lower, in COVID (+) patients compared to the control group (see Tab. 2). There was no statistically significant difference in D-dimer level, but this may be due to the fact that it is not routinely assessed in COVID (–) stroke patients in our centre, in fact only when thrombosis is suspected. It was impossible to compare fibrinogen levels due to the small data sample.

All our results are summarised in Table 2.

Discussion

To the best of our knowledge, this study is the first in Poland to present the characteristics of patients with COVID-19-associated AIS after MT. It is also the first study to compare stroke size in MT-treated patients with and without COVID-19 using CT-perfusion imaging with post-processing analysis with RAPID software.

LAO in COVID-19 patients seems to be associated with higher mortality than in patients without SARS-CoV2 infection [6]. However, previous studies on the outcomes of COVID-19 patients treated with MT produced mixed results, as presented in a recent systematic review [8]. Some of the research has shown poor outcomes in such patients.

A study by Escalard et al. including 10 patients showed an in-hospital mortality rate of 60% [15]. A recent multicentre study by Cagnazzo et al. which included 93 COVID (+) patients showed a 30-day mortality of 29% [16]. A study by Pop et al. involving 13 COVID (+) patients reported mortality of 15.3% and a high incidence of in-hospital thrombotic complications in this group [17].

On the other hand, some studies have reported similar outcomes of COVID (+) and COVID (–) patients. A prospective international study by al Kasab et al. compared 13 COVID (+) MT-treated patients to a group of 445 COVID (–) MT-treated patients. This revealed that patients with a SARS-CoV2 infection had a higher NIHSS score at admission but did not differ in respect to in-hospital mortality, number of days of hospitalisation, or functional outcome measured with mRS at discharge. At the same time, COVID (+) patients were significantly younger than COVID (–) ones, which may have influenced the results [18].

In our study, the MT-treated AIS patients with a SARS CoV2 infection also presented with similar outcomes to patients without COVID-19 (including mortality 6.7% vs. 12.6%). We speculate that this may be due to several reasons. Firstly, there were no clinical differences at admission parameters between our COVID (+) and COVID (–) MT-treated AIS patients. There was a similar age distribution, gender ratio, and number of cardiovascular risk factors. Moreover, there were no significant differences in stroke volume (as counted by perfusion CT analysis with RAPID software). Secondly, there was no statistically significant difference between groups when it came to the time from stroke onset to arrival at the CSC. The difference between groups concerning time from arrival at the CSC to groin puncture was statistically significant, but small. This is probably due to the standardised pathway of care that was implemented for both groups of patients during the pandemic, including a separate part of the Emergency Department and CT laboratory, as well as transport pathways for COVID (+) patients. Thirdly, after the procedure both groups of patients were treated in highly specialised wards (the Stroke Unit or the Neurology/COVID-19 ward) with specialists trained in stroke care present in both of them. What is more, good outcomes of our patients may also be a result of their relatively mild COVID-19 course. None of our patients required intensive care or mechanical ventilation. In 2020 and 2021 (up to the time of writing), there were seven disqualifications of COVID (+) patients from mechanical thrombectomy in our centre, and none of the seven was due to severe general condition caused by COVID-19; they were all based on the neurological criteria. Four patients were disqualified due to recanalisation of the artery after intravenous

thrombolysis, two patients due to predominance of irreversible ischaemic changes in neuroimaging, and one patient due to haemorrhagic transformation of the stroke.

Our study has some limitations. Firstly, it was a retrospective analysis and the study group was relatively small. Secondly, the patients had a mild-to-moderate COVID-19 course which might also have an important impact on their outcomes. Thirdly, the small group of patients with COVID-19 treated with MT did not allow for multivariable analysis.

Clinical implications / future directions

Our research suggests that in patients with MT-treated AIS associated with COVID-19 who do not require intensive care, the outcome may be similar to that in MT-treated AIS without concomitant SARS-CoV2 infection. Not only the patients' clinical profiles, but also efficient organisation and the implementation of standardised pathways of care, seem to play important roles in the final result of the treatment.

The outcomes of COVID-19-associated AIS patients treated with MT should be reported in larger, and preferably prospective and multicentre, studies.

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