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Clinical short communication

Impact of SARS-CoV-2 infection on acute intracerebral haemorrhage in northern Italy

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ABSTRACT

Introduction: Growing evidence has been published as to the impact of SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) on cerebrovascular events over the last few months, with considerable attention paid to ischemic strokes. Conversely, little is known about the clinical course of intracerebral haemorrhage (ICH) and simultaneous SARS-CoV-2 infection.

Method: The Italian Society of Hospital Neurosciences (SNO) promoted a multicentre, retrospective, observational study (SNO-COVID-19), involving 20 Neurological Departments in Northern Italy. Clinical data on patients with acute cerebrovascular diseases, admitted from March 1st to April 30th, 2020, were collected. A comparison was made of the demographical and clinical features of both SARS-CoV-2 positive and negative patients with ICH.

Results: 949 patients were enrolled (average age 73.4 years; 52.7% males); 135 patients had haemorrhagic stroke and 127 (13.4%) had a primary ICH. Only 16 patients with ICH (12.6%) had laboratory confirmed SARS-CoV-2 infection, both symptomatic and asymptomatic. SARS-CoV-2 related pneumonia or respiratory distress (OR 5.4), lobar location (OR 5.0) and previous antiplatelet or anticoagulant treatment (OR 2.9) were the only factors

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significantly associated with increased mortality in ICH. SARS-CoV-2 infection, regardless of respiratory involvement, led to a non-significantly increased risk of in-hospital death (37.5% vs 23.4%, $p = 0.2$).
Discussion: ICH patients with COVID-19 did not experience an increase in mortality as striking as ischemic stroke. The inflammatory response and respiratory complications could justify the slight increase of death in ICH. Bleeding sites and previous antiplatelet or anticoagulant treatment were the only other predictors of a worse outcome.

1. Introduction

In the last few days of February 2020, an extensive outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) involved Northern Italy. In the two months that followed, the disease caused by SARS-CoV-2, named COVID-19 [1], spread quickly. The spectrum of SARS-CoV-2 infection severity varied widely and a substantial number of patients had neurological manifestations [2–4]. Particularly, evidence is emerging concerning both the frequency and the outcome of cerebrovascular complications. One of the first single centre studies described a 4.6% risk of ischemic stroke and a 0.5% risk of intracerebral haemorrhage in patients with COVID-19 [5]. Further analysis estimated the occurrence of cerebrovascular events in COVID-19 patients, ranging from 0.9% to 1.8% [6–8]. The proportion of ischaemic versus haemorrhagic strokes is not significantly skewed as compared to the pre-COVID-19 era or to SARS-CoV-2 negative patients admitted to hospitals during the pandemic. Conversely, a striking increase in intra-hospital mortality is being reported, especially for SARS-CoV-2 positive patients affected by ischaemic stroke, whereas data for haemorrhagic stroke are scanty [8]. The increased risk of stroke and mortality in systemic infection is not exclusive to SARS-CoV-2: early changes of clotting, platelet activation and artery dysfunction during severe sepsis may be involved in thrombotic-related events and act as additional risk factors [9].

Our study addressed the clinical course of patients with cerebral haemorrhage and simultaneous SARS-CoV-2 infection, paying particular attention to both SARS-CoV-2 positive and negative patients hospitalized during the pandemic.

2. Methods

2.1. Study design

The Italian Society of Hospital Neurosciences (SNO) promoted a multicentre, retrospective, observational study (SNO-COVID-19), involving 20 Neurological Departments in Northern Italy. Nineteen were in Lombardy region, the most affected area in Italy, and one centre was in the neighbouring region of Emilia. It included both hospitals designated as hubs for cerebrovascular diseases and those promptly converted into predominantly COVID-19 Hospitals.

Data were collected on patients consecutively admitted to neurological departments, from March 1st to April 30th, 2020, with cerebrovascular diseases, occurring either at home or during hospitalization for other causes. The following main diagnoses were included: ischemic stroke, primary intracerebral haemorrhage (ICH), subarachnoid haemorrhage and cerebral venous thrombosis. Herein, the focus is on patients with spontaneous ICH in both SARS-CoV-2 positive and negative patients. A comparison was made of the demographical and clinical features, including in-hospital outcome.

Due to the limitations of resources during the first few months, only patients with a suggestive history or with clinical or radiological signs were screened by nasal swabs. SARS-CoV-2 infection was confirmed by real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) on the nasopharyngeal specimens or on bronchoalveolar lavage (BAL), whenever there was a high clinical suspicion of SARS-CoV-2 infection but a negative nasal swab.

Ethical approval for the study was obtained from the Local Research Ethics Committee and the single Ethical Committees of participating centres.

2.2. Data collection and statistical analysis

Patient information was collected for age and gender, type of cerebrovascular accident, with OCSP or TOAST classification of ischemic stroke [10,11], whereas lobar or typical location was considered for ICH; hematologic parameters (CRP, D-dimer and total lymphocyte count), previous antiplatelet or anticoagulant drugs, functional outcome at discharge (using a four-grade scale) and discharge arrangement. Information about COVID-19 was also included: incidental or symptomatic finding of SARS-CoV-2, extent of pulmonary involvement, whether continuous positive airway pressure (CPAP) and/or endotracheal tube was required, neuropsychiatric symptoms and the cause of death. The local investigators provided the coordinating centre ("Alessandro Manzoni" Hospital) with all the data for analysis.

Statistical analyses were performed by descriptive statistics and chi-square test. Multivariate analysis was performed on mortality outcome and predictors were variables significant with $p < 0.1$ at univariate testing with a backward selection based on likelihood ratio to find the most parsimonious model. Analyses were performed with IBM SPSS software version 26.0.

3. Results

From March 1st to April 30th, 2020, 949 patients [average age 73.4 years; median age 76 years. 500 males (52.7%)] were admitted to the study hospitals for a cerebrovascular accident. 127 (13.4%) were diagnosed with ICH. The average age for ICH was 74.5 ± 11.6 (range 34–95 years), 68 (53.5%) were female and 58 (45.7%) had typical ICH (Fig. 1). Among all ICH patients, 16 (12.6%) were diagnosed as SARS-CoV-2 positive by nasopharyngeal swab: 6 patients were asymptomatic cases of COVID-19 infection. There were no gender differences. The outcome in SARS-CoV-2 positive patients was generally worse, but not to a statistically significant extent: 1 (6.3%) was discharged without any symptoms, 5 (31.3%) with mild disability but able to walk, 4 (25%) unable to walk even with assistance. In the group of negative patients, 16 (14.4%) were discharged without any symptoms, 31 (27.9%) with mild disability but able to walk, 38 (34.2%) unable to walk even with assistance. Only 32 patients (25.2%) died during hospitalization: 6 patients were SARS-CoV-2 positive (37.5%), 26 were negative patients (23.4%). The difference was not statistically significant (OR 1.96; 95% CI: 0.65–5.91; $p = 0.2$).

The most common ICH was lobar, 69 patients (54.3%), 9 of them tested positive for SARS-CoV-2. 58 patients (45.7%) had a typical ICH and only 7 a concomitant SARS-CoV-2 infection. In-hospital death rate was significantly higher in lobar than in typical ICH patients (37.7% vs 10.3%; OR 5.24; 95% CI: 1.9–13.9; $p = 0.001$). Mortality was also increased in older patients (13.6% in <65 years, 14.5% in 65–80 years, 42% in >80 years; $p = 0.03$) and in those previously treated with antiplatelet or anticoagulant drugs (14% in the "no treatment group", 31.9% in patients on antiplatelet therapy, 44.4% in those on anticoagulant. OR of patients with previous treatment 3.3; 95% CI: 1.3–8.4, $p = 0.01$). Positivity for SARS-CoV-2 did not seem to affect these differences. A higher percentage of SARS-CoV-2 positive patients had markedly elevated CRP and D-dimer levels than negative patients ($p = 0.04$): fivefold threshold limit CRP values were associated with increased

mortality in COVID-19 patients (60% vs 27.3%; OR 4.0; 95% CI: 0.43–37.1; $p = 0.21$), while lymphopenia was not (25% vs 36.4%; OR 0.58; 95% CI: 0.04–7.66; $p = 0.7$). Elevated D-dimer levels (measured in 63 subjects) were associated with higher mortality (OR 5.2; 95% CI: 1.5–17.1; $p = 0.007$), regardless of SARS-CoV-2 status.

The need for respiratory support had a negative impact on the prognosis: 8 patients required CPAP and 7 were eventually intubated. Most deaths in SARS-CoV-2 patients occurred in the severe pneumonia and respiratory distress group (4/7 died: 57.1%), while only 2 patients out of 9 (22%) died in the group with no or mild disease (OR 4.4; 95% CI: 0.9–0.20.8, $p = 0.06$). COVID-19 was not associated with a higher incidence of delirium, but delirium was associated with death (40% vs 25.8%), although without statistical significance. Multivariate analysis confirmed a significant impact on mortality of lobar location (OR 5.0;

a. Clinical features of SARS-CoV-2 positive and negative patients

	SARS-CoV-2 positive (16 pts)	SARS-CoV-2 negative (111 pts)	p
Age	79.1 (±10.7)	73.8 (±11.6)	
<65 / 65-80 / >80 years	3/5/8	19/50/42	0.56
Sex (M:F)	7:9	52:59	0.82
Clinical			
Location (typical/lobar)	7(43.8%) / 9(56.2%)	51(45.9%) / 60(54.1%)	0.86
No treatment/Antiplatelet/anticoagulant	8(53.3%) / 4(26.7%) / 3(20%)	42(42%) / 43(43%) / 15(15%)	0.49
Symptomatic/asymptomatic COVID-19	10/6	*	*
Delirium	2 (13.3%)	13 (14%)	0.95
CRP (normal or <5 x UNL / > 5 x UNL)	11(68.8%) / 5(31.3%)	95(88.8%) / 12(11.2%)	**0.03**
Lymphopenia	4 (26.7%)	24 (23.5%)	0.79
D-dimer (> 2 x UNL)	8 (66.6%)	15 (29.4%)	**0.02**
Outcome			
No symptoms	1 (6.3%)	16 (14.4%)	0.5
Mild disability (able to walk)	5 (31.3%)	31 (27.9%)	
Severe disability (unable to walk)	4 (25%)	38 (34.2%)	
Death	6 (37.5%)	26 (23.4%)	
Discharge Destination			
Own home	2 (12.5%)	24 (22%)	0.5
Geriatric/Rehab	8 (50%)	54 (49.5%)	
Nursing Home (and other special facilities)	0 (0%)	5 (4.6%)	
Death	6 (37.5%)	26 (23.9%)	

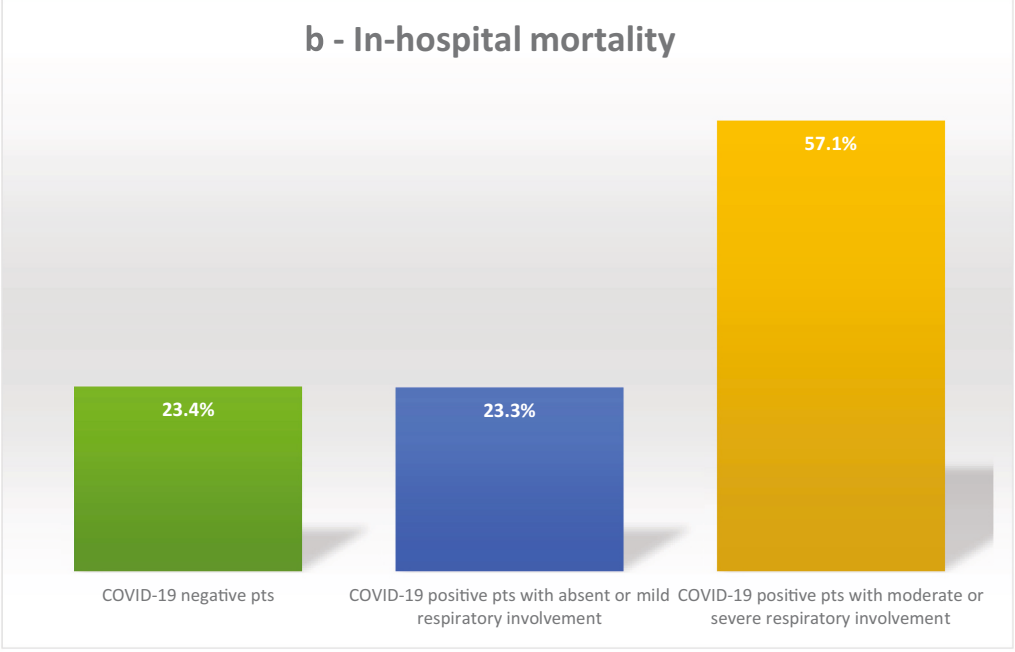

Fig. 1. a. Clinical and demographical features of SARS-CoV-2 negative and positive patients. The percentages were calculated on the total number of patients for whom that item was available. **1b.** In-Hospital mortality index in SARS-CoV-2 negative and positive patients. SARS-CoV-2 positive patients were subdivided by respiratory involvement.

95% CI: 1.8–14.1; $p = 0.002$), previous anticoagulant or antiplatelet treatment (OR 2.9; 95% CI: 1.1–8.2; $p = 0.03$) and respiratory distress in SARS-CoV-2 positive subjects (OR 5.4; 95% CI: 0.8–28.5; $p = 0.06$) (Fig. 2).

4. Discussion

The increased mortality during hospitalization in patients with ICH and COVID-19 was not as marked as that observed in ischaemic stroke [6,8] or myocardial infarction [12], despite ICH mortality is known to be higher compared to other cerebrovascular diseases [13]. This finding is also strikingly different from patients with acute ischemic stroke recruited in our study in the same period, whose mortality was increased fourfold by COVID-19. Inflammation, hypoxia and pro-thrombotic activity linked to SARS-CoV-2 may play a relevant role in the clinical and biological evolution of tissue damage, and this role may be more prominent in ischaemic than in haemorrhagic stroke [14,15], despite recent evidence of multiple cerebral microbleeds in critically ill or deceased COVID-19 patients [16]. In our cohort a massive inflammatory response with increased CRP values appeared to be related with a worse prognosis in SARS-CoV-2 patients, while elevated D-dimer levels increased mortality risk in both SARS-CoV-2 positive and negative patients. Nonetheless, this response did not affect the incidence of delirium in COVID-19 patients. This finding might be related to the comparatively low number of patients with SARS-CoV-2 infection included or it might also suggest that systemic inflammation in the context of COVID-19 impact less severely on haemorrhagic cerebral lesions [6,8]. Delirium in SARS-CoV-2 infection is probably a heterogeneous entity, encompassing rare cases of true encephalitis and more frequent cases of encephalopathy: a recent report underscored the relevance of cytokine release within the CNS (TNF-α, IL-6 and IL-8 levels in the CSF) in the differential diagnosis between COVID-19 encephalopathy and encephalitis [17]. Despite multiple pathways allowing potential entry into the CNS of the virus (viremia, trans-nasal and retrograde axonal transport in neurons), most neuropathology studies have failed to detect virus in all the patients with neuropsychiatric symptoms.

During the COVID-19 outbreak, reduced/delayed admissions for cerebrovascular events [18] and pandemic-induced constraints in availability of diagnostic and therapeutic facilities might have contributed to increase mortality for cerebrovascular accidents. However, as most studies carried out on stroke and COVID-19 have no internal control groups or historical data to count on, it is not possible to make a precise evaluation of the impact these factors have [19]. Conversely, our study provides an internal control group of SARS-CoV-2 negative patients with ICH admitted to neurology units in the same period, thus eliminating pandemic-related changes in overall mortality. In our cohort, in-hospital mortality in ICH was low, and gender distribution

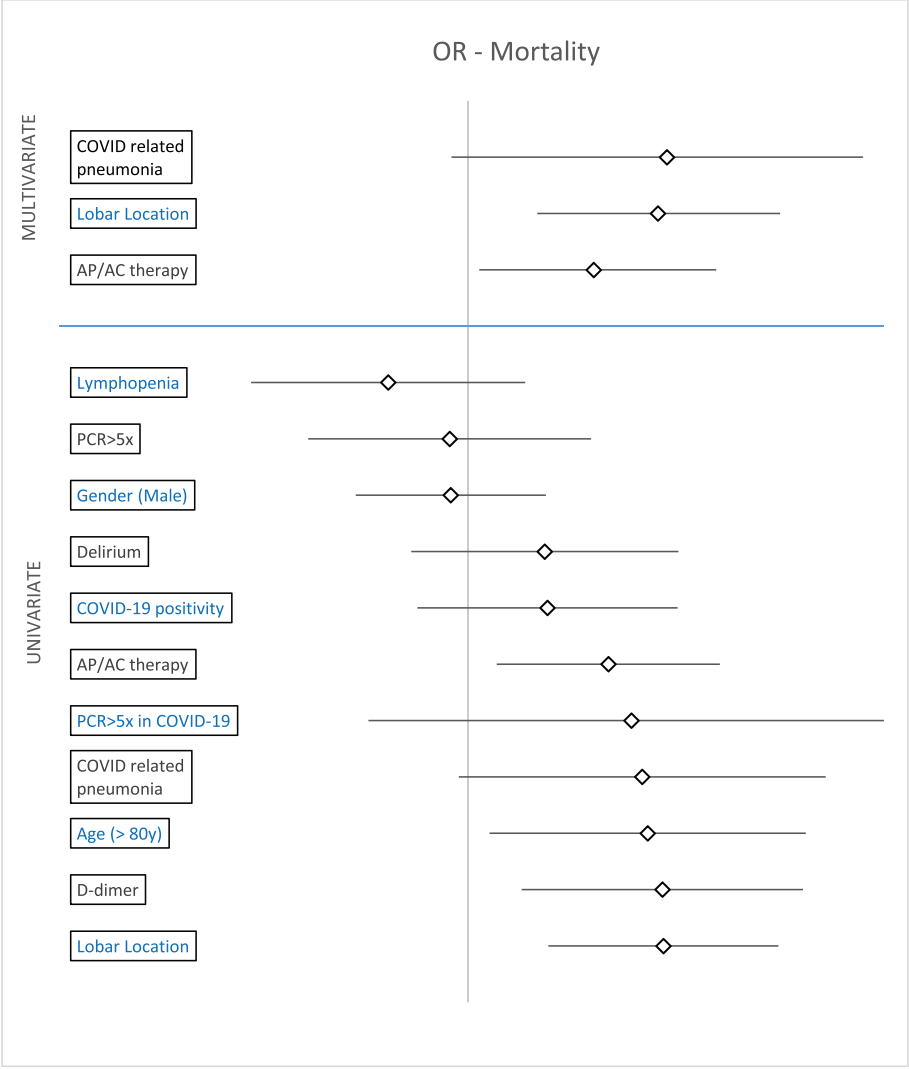

Fig. 2. Multivariate analysis on mortality outcome of the main variables significant with $p < 0.1$ at univariate testing and with complete data collection.

and haemorrhage location were not significantly different in SARS-CoV-2 patients [8]. These findings may be partially explained by our recruitment strategy from neurological departments with a possible under-diagnosis of brain haemorrhages occurring in seriously ill patients admitted to acute non-neurological care wards and Intensive Care Unit for COVID-19.

Overall, as is well known, our study confirms that age, ICH sites and previous antiplatelet or anticoagulant treatment are predictors of in-hospital death. Unlike ischemic stroke, ICH in SARS-CoV-2 patients led only to a slight increase in mortality, mainly due to respiratory involvement, whilst bleeding location, previous therapies and gender do not seem to impact differently in SARS-CoV-2 positive and negative patients. Additional studies are needed to definitely prove the dissimilar effect of COVID-19 in different cerebrovascular diseases.

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Ethics approval

Ethical approval for the study was obtained from the Local Research Ethics Committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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