REVIEW

Stroke epidemiology and COVID-19 pandemic

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Purpose of review
The aim of this study was to describe the impact of the COVID-19 outbreak on the epidemiology, cause and clinical characteristics of incident stroke in different settings and populations.

Recent findings
Several studies have shown that there are three main themes in the epidemiology of stroke during the COVID-19 pandemic: COVID-19 seems to be associated with stroke in a significant number of patients. This association has been reported in several clinical series, mainly from China. There is a consistent trend towards a decreased number of hospital admissions of stroke patients during the pandemic. There are no population-based data available on incident stroke in individuals with COVID-19.

Summary
In this review, we report on increased rates and severe prognosis of ischemic stroke among individuals with COVID-19, probably explained by hypercoagulability and inflammation, documented since the early phase of disease.
We confirm the presence of falling rates of new ischemic stroke admissions in hospitals, probably due to social consequences of the pandemic: fear to be infected or not adequately treated in the hospital. This phenomenon is restricted to mild stroke and transient ischemic attacks.
Short and long-term consequences of this trend of new strokes in the pandemic need to be evaluated.

Keywords
community studies, COVID19, epidemiology, pandemic, registries, stroke

INTRODUCTION

The novel human coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was first discovered in the region of Wuhan, China in December of 2019 and has led in few weeks to a pandemic, as it was declared by the WHO on 11 March 2020. In COVID-19 clinical features, neurological symptoms are highly prevalent and heterogeneous, including anosmia and hypogeusia, seizures and strokes.

Several studies have shown that the COVID-19 outbreak had a relevant impact not only on the epidemiology but also on the specific cause of incident stroke.

There are three main themes to be addressed in the emergency on the relationship between stroke and COVID-19 pandemic:

(1) COVID-19 seems to be associated with a stroke in a significant number of patients. This association has been reported in several clinical series, mainly from China.
(2) There is a consistent trend towards a decreased number of admittances of stroke patients to hospitals during the pandemic.
(3) There are no population-based data available on the onset of stroke in individuals with COVID-19.

STROKE INCREASED RATES IN INDIVIDUALS WITH COVID-19

Neurological manifestations can occur early in the course of COVID-19, at the time of diagnosis as initial symptom(s). This is true especially for non-specific symptoms such as headache, nausea and dizziness. Myalgia (11%), confusion (9%) and

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Curr Opin Neurol 2021, 34:3–10
DOI:10.1097/WCO.0000000000000879

KEY POINTS

- There is evidence suggesting a high rate of cerebrovascular complications in patients with SARS-CoV-2 infection especially among patients with comorbidities or vascular risk factors, with a worse prognosis compared with other covid-19 patients.
- Stroke cases are characterized by high levels of biomarkers of inflammatory response (high level of neutrophils and IL-6) and coagulation defects (high level of D-Dimer and low platelet count).
- Falling rates of new ischemic stroke admissions and diagnoses in medical institutions during the pandemic have been reported, particularly among mild strokes.
- The falling rates are probably linked to the social consequence of the pandemic: fear to be infected if going to the hospital, limited transport availability, lack of family support and medical personnel shortage.
- Stroke, even during the pandemic, is still a time-dependent disease and healthcare systems need to be preserved providing at the same time safety measures for health providers and patients.

headache (8%) have been also reported in an early series of 99 patients from Wuhan [1]. In a large series from a Spanish hospital, 841 patients [2], neurological manifestations related to COVID-19 such as myalgia (17.2%), headache (14.1%) and dizziness (6.1%) appeared early in a large number of patients. Impairment of smell or taste (hypogeusia and anosmia) appeared early as well, especially in less severe patients. Later, specific neurologic symptoms and syndromes with lower prevalence appear, including myopathies, polyneuropathies, limb weakness, seizures and acute cerebrovascular diseases. Neurological symptoms are therefore common (56%) in COVID-19 and highly heterogeneous, with cerebrovascular disease generally developing later, after the first 2 weeks, secondary to the development of the increased hypercoagulable and inflammation state [3,4]. However, sometimes, a cerebrovascular disease appears early during the disease course. A series of five patients with large vessel disease as initial symptom of COVID-19 was described in New York City [5]. The mean NIHSS score in this series was 17 that indicates a severe disability. According to the authors, this severe disability was partly due to the delayed referral to the hospital because of fear of contagion among patients and their families.

In a case series of individuals admitted to a Wuhan hospital during the emergency [6], almost 40% of patients presented neurological symptoms and 3% (six patients) presented stroke. Out of six strokes, five were ischemic and only one was haemorrhagic. Neurologic symptoms and complications such as cerebrovascular diseases, consciousness impairment and skeletal muscle symptoms were more likely in severe patients.

In a major report from a single institution in Wuhan [7], China, out of 1875 patients, 50 (2.6%) were diagnosed as stroke, with higher prevalence of ischemic lesions (90%). The authors used propensity score to match and compare survival in COVID-19 patients with and without a history of stroke. Stroke patients were more likely to die and to have mechanical ventilation. Patients with a history of stroke tended to have comorbidities or vascular risk factors (hypertension, pulmonary diseases and smoking), high levels of biomarkers of inflammatory response (high level of neutrophils and IL-6) and coagulation defects (high level of D-Dimer and low platelet count). However, after adjusting with propensity scores, stroke patients were still more likely to have a negative outcome.

In a retrospective evaluation of the neurologic features of 58 out of 64 consecutive patients admitted to two ICUs in Strasbourg [8], France, because of acute respiratory distress syndrome (ARDS) due to COVID-19, three out of 13 (23%) patients undergoing MRI had ischemic stroke, while 11 out of 13 who underwent perfusion MRI presented bilateral hypoperfusion of frontotemporal lobes. This series focused on severe patients, including patients with loss of consciousness, and this may be responsible for the high rate of ischemic strokes.

In a retrospective study conducted in New York [9▪], COVID-19 patients with stroke were compared with noninfected stroke patients. The most interesting finding is that cryptogenic stroke was extremely most common in patients with COVID-19 infection (65.6%). The prevalence of imaging-confirmed stroke was only 0.9%, lower than rates of imaging-confirmed strokes in China. The prognosis of stroke patients with COVID-19 was extremely severe with 80% needing mechanical ventilation.

This study confirms other observations reporting a lower number of stroke admissions probably because of fear of contagion and behaviours suggesting the avoidance of hospital access for mild stroke. COVID-19 positive individuals presented cryptogenic strokes probably due to a status of hypercoagulability, measured with high D-dimer levels.

In general, it is also true that the severity of the primary respiratory syndrome and the risk of negative prognosis in COVID-19 patients with stroke differ in individuals with preexisting cardiovascular diseases [10]. These data may indicate that the presence of respiratory distress and other indicators of systemic severity may favour the onset of neurologic complications.

Another interesting question is the possibly increased rate of stroke during COVID-19 compared with the rate of stroke in other influenza virus infections.

In a retrospective cohort study conducted in two academic centres in New York City [11▪], among 1916 individuals admitted with COVID-19 in the period from 4 March 2020 through 2 May 2020, 31 (1.6%) had an acute ischemic stroke, while three (0.2%) out of 1486 patients with influenza A/B, ascertained through laboratory testing, had an acute ischemic stroke in the period between 1 January 2016, and 31 May 2018 [odds ratio, 7.6; 95% confidence interval (95% CI), 2.3–25.2] after adjusting for multiple confounders such as age, stroke and race. Therefore, patients with COVID-19 have a significantly increased risk of acute ischemic stroke compared with patients with influenza. This study was possible because all ischemic stroke cases were incepted through a registry system named CAESAR (Cornell Acute Ischemic Stroke Center) that enrolled stroke cases over all the period of observation.

The increased risk of thromboembolic events in severely ill patients is confirmed in reports from three hospitals in the Netherlands [12]. The cumulative incidence of the composite thromboembolic outcome, adjusted for competing risks of death, over a median follow-up period of 14 days, was 49% with 75 events in 184 patients. In this series, most thrombotic events were pulmonary embolism and five were ischemic stroke (2.7%). Patients with thrombotic complications in this series had a five-fold increased risk of death.

In a larger series (388 patients from an academic hospital in Italy admitted to the ICU), the cumulative incidence rate of thromboembolic events was 21%, while the rate of ischemic stroke was 2.5% [13]. This study confirms the high rate of thromboembolic events but underlines that this can be an underestimation due to the relatively low number of imaging studies performed. The prognosis was particularly serious in these patients, particularly in those with high levels of D-Dimer.

ONGOING SURVEILLANCE SYSTEMS AND STROKE EPIDEMIOLOGY IN THE PANDEMIC ERA

The Global Burden of Disease (GBD) Collaboration has developed projections of contagions, deaths and resource utilization in response to the COVID-19 pandemic (https://covid19.healthdata.org/united-states-of-america). For the projected estimates, the GBD Collaboration primarily uses the COVID-19 cases and deaths obtained from local and national governments, hospital networks and associations, the WHO, third-party aggregators and a range of other sources. The world COVID-19 data are aggregated and continuously updated by the Johns Hopkins University data repository. Findings on daily infections and testing, hospital resource use and deaths are presented for the USA and several European and non-European countries from the start of the outbreak with projections until 1 November 2020. In making these forecasts, policymakers can be assisted to plan and take action to change the course of the pandemic for the better. The GBD Collaboration will also provide the background information before, during and after the outbreak to assess the geographic and temporal trends of this burden for each clinical condition identified in the GBD (including stroke) at a global, regional, national and eventually subnational level.

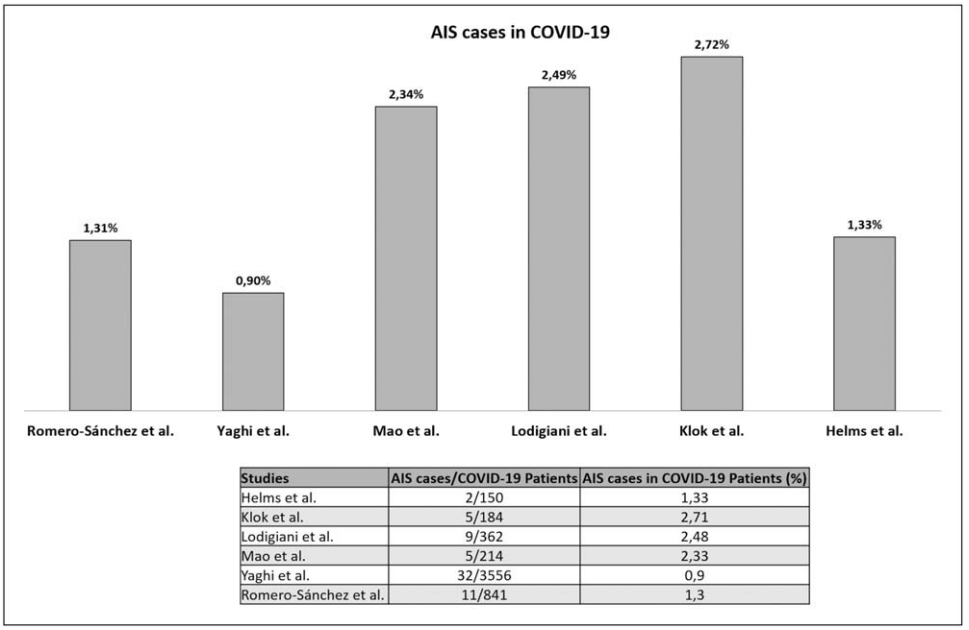
A clinic-based registry has been activated, promoted by the European Academy of Neurology (EAN) to define the incidence of stroke and other neurological manifestations during and after the COVID-19 outbreak in various European countries. In addition, the EAN and the US Neurocritical Care Society established a formal collaboration for the harmonization of data collection to establish a synergistic and systematic approach for the reporting of the frequency, severity and outcome of neurological manifestations.

This collaboration, along with several other ongoing national and local surveillance programmes, might help to define the estimated number of patients with stroke coming to medical attention in various settings, the place of their first assessment, their management and outcome.

In conclusion, the COVID-19 pandemic seems to be associated with elevated risk of ischemic stroke and thromboembolic events in general. Inflammation-induced hypercoagulability in the early phase and subsequent local and general embolism in COVID-19 stroke patients need both clinical and laboratory investigations. Stroke is associated with a severe prognosis in individuals with COVID-19. These results are based upon clinical series and are heterogeneous (Fig. 1). There are no population-based studies on this issue so far.

Previous coronavirus outbreaks have been associated with a significant burden of cardiovascular comorbidities and complications. This increases the prevalence of key risk factors for stroke. In a previous report on SARS and in COVID-19, arrhythmia, shock and cardiac injury were present with the highest reported prevalence in individuals hospitalized in an ICU [14].

Association of cardiovascular morbidity and mortality has been described as one of the long-term



Studies	AIS cases/COVID-19 Patients	AIS cases in COVID-19 Patients (%)
Helms et al.	2/150	1,33
Klok et al.	5/184	2,71
Lodigiani et al.	9/362	2,48
Mao et al.	5/214	2,33
Yaghi et al.	32/3556	0,9
Romero-Sánchez et al.	11/841	1,3

FIGURE 1. Ischemic stroke percentages among COVID-19 admissions in clinical series.

consequences of hospitalization for pneumonia [15]. Long-term prognosis following outbreaks of respiratory virus infection may equally depend upon the extra-pulmonary manifestations including cerebrovascular and cardiovascular morbidities.

LOW REFERRAL AND REPORTING OF STROKES DURING THE COVID 19 EPIDEMIC

Although there is evidence suggesting a high rate of cerebrovascular complications in patients with SARS-CoV-2 infection [3,6], a series of reports indicate possible falling rates of new ischemic stroke admissions and diagnoses in medical institutions during the pandemic; patients are less likely to go to hospitals to ask for medical assistance, even in the presence of mild but unequivocal symptoms of stroke. This phenomenon has been episodically reported in the media both for stroke and cardiac patients (https://www.tctmd.com/news/mystery-missing-stemis-during-covid-19-pandemic, https://www.washingtonpost.com/national/health-science/hospital-admissions-for-strokes appear-to-have-plummeted-a-doctors-says-a-possible-sign-people-are-afraidto- seek-critical-help 2020/04/08/2048b886-79ac-11eab6ff-597f170df8f8_story.html). To avoid the spread of the epidemic, governments and public health officials have issued several measures restricting access to public places including hospitals and encouraging physical distance.

There are several reports from single centres examining the phenomenon of missing strokes. In a tertiary centre in New Jersey, Siegler *et al.* [16] compared the stroke frequency based on referral to the Cooper University Hospital (CUH), a comprehensive stroke centre that serves five Primary Stroke Centers in southern New Jersey, and compared two periods, 1 October 2019 to 29 February 2020 (Pre-Covid) and 1 March to April 15 (COVID-19 epidemic period). 1st March was the critical day because in that day the first New Jersey resident with COVID-19 was diagnosed after appropriate testing. Between the two periods, there was a mean fall of about 40% in new stroke diagnoses, 55% fewer patients presenting directly to the institution by private vehicle and 29% fewer patients through emergency services, 60% less transfers from other hospitals and 25% less teleconsults [16]. Interestingly, there was a higher proportion of individuals with large vessel occlusion but no change in the absolute numbers.

This phenomenon is probably linked to the social consequence of the pandemic: fear to be infected if going to the hospital; the unchanged number of severe strokes in this statistic (number of long vessel occlusions) enforces the idea that an erroneous perception of the consequence of the pandemic is the leading cause of changes in stroke referrals. Severe cases continue to go to hospitals while mild cases do not. In the same period, the mortality rate in that series (21% after 2.5 days in hospital) [16] was higher than the reported mortality in observational studies and in the placebo arm of stroke randomized clinical trials. Another explanation of the decreased number of requests for medical services may be the worries due to lack of

health insurance coverage of medical services because of the social consequences of the pandemic (fall of employment rates). On the positive site, during the pandemic, there was a reported shorter time (9 min less) to thrombolysis [16], even in presence of severe measures against contamination for anybody in health services that made all the transitions during the service more complex.

All these data support the idea that individuals with milder stroke symptoms were intentionally avoiding to seek medical care. Another issue is the diminished use of MRI in the stroke diagnosis. This could have determined a number of missed diagnoses of milder ischemic stroke, if computed tomography (CT) scan was the only imaging technique used for diagnosis. This has consequences both on counting the number of new strokes for epidemiological studies and underestimating the disabilities due to stroke. Similar results have been reported in a stroke population-based registry in Joinville, in southern Brazil, an area of 590 466 inhabitants with 80% of stroke cases referred to the main hospital of the area (Hospital Municipal São José) [17▪▪]. The critical day was 17 March because it was the starting date for social restrictions after the first COVID-19 diagnosis in the city on 13 March. Even in absence of national measures, in the city of Joinville, all social activities were restricted with stop to educational, economic, social activities and public transportations, including the closing of bars and restaurants. A decrease in total stroke admissions was present going from an average of 12.9/100 000 per month in 2019 to 8.3 after COVID-19. Overall, there was a 36% decrease, represented by transient ischemic attacks (TIAs), mild and moderate strokes while severe stroke rates remained unchanged. The strength of this work is the presence of a population-based registry. The authors used a system already in place with the same protocol and no changes in the referral policies for stroke patients.

The most extensive report of changes in the healthcare stroke system is from the Big Data Observatory Platform for Stroke of China [18▪▪], a network of 280 hospitals, with thrombolyses and thrombectomies falling by 26.7 and 25.3%, respectively, comparing February 2020 with February 2019. Despite a small increase in the rates of the two procedures in the same period based on admissions, in the 227 hospitals that provided the data for this survey, stroke beds were drastically reduced (50% assigned to COVID-19 management). However, it is important to underline that, even during the peak of the epidemic, only a small percentage of hospitals closed the fast channels for stroke care. The authors calculate that about 13 000 less stroke patients were admitted to the hospitals accounting for more than 1000 less thrombolyses and almost 400 less thrombectomies. The major factor also in China is that patients and their families were inclined to avoid the hospitals during the epidemic. Beyond fear of contagion, limited transport availability, lack of family support because of social isolation and distancing, and medical personnel shortage were additional factors that probably played a role on the drop of stroke cases. The lack of stroke awareness played a major role (second factor in ranking) as in the pre COVID-19 period. These numbers predict a huge impact of stroke during COVID-19 with health consequences as lack of secondary prevention and long-term disabilities.

Similar changes of referrals for stroke have been reported for cardiac patients; several studies in Europe have reported a decreased number of patients admitted to hospitals for ST-segment elevation myocardial infarction (STEMI) since the COVID-19 pandemic onset. In Austria, a 40% decrease in hospital admissions for acute coronary syndrome has been reported tracking cases in 17 out of 19 national centres for public primary percutaneous coronary intervention (PCI) [19]. There are many possible reasons for this trend: the overload of the emergency systems, the decrease in attention and awareness to specific medical emergencies not due to COVID-19, and the fear of infection. Finally, another possible clue is the decreased expectation to receive the proper treatment in overloaded emergency services [20].

Similar trends have been reported during the SARS 2 epidemic. In South Korea, during the peak of the epidemic (June 2015), the number of emergency visits decreased by more than 30% especially for low-intensity emergencies such as otitis and upper respiratory infection [21]. In the same period, referrals for both stroke and myocardial infarction decreased by about 15%.

CONCLUSION AND FUTURE DIRECTIONS

On the basis of the COVID-19 experience, the outpatient diagnostic tests and the use of teleconsults should be both expanded. This shift in medical care could prevent in the future some of the worries due to referral to the hospitals of suspected stroke cases. The efficacy of this shift could be tested in future population-based studies.

The rigorous public health measures, which are undoubtedly needed to control the COVID-19 pandemic, may have determined unpredictable failures in the integrated care emergency systems.

There are two sites of stroke epidemiology that need to be considered: the increased risk of stroke for patients with COVID-19 and the missing stroke cases due to lack of referral. These two different

phenomena may determine an unprecedented increase in morbidity and mortality due directly and indirectly to cerebrovascular disease during the COVID-19 epidemic. To evaluate at best the long-term consequences, we need cohort studies in a defined setting, preferably population based. This type of approach with longitudinal studies in defined settings such as schools, workplaces and communities have been advocated for the study of COVID-19 epidemiology [22] in the early phase of pandemic. To improve our understanding, we need to study COVID-19 with designs wherein there is a clear identification of denominators (populations at risk) and numerators (cases). This epidemiological methodology has been extensively used in stroke population-based registries. This approach offers the possibility to identify the denominator and with extensive laboratory testing to identify at population level COVID-19 cases with strokes. The population-based registry methodology has been successfully used in several settings and for neurological diseases, including chronic and rare [23] and acute and common as strokes, even at national levels [24]. In the only population-based studies with a stroke registry, we have an estimate of decrease of stroke admissions in the general population in a Brazilian town [17▪▪].

One unpredicted consequence of COVID-19 pandemic might be a substantial increase in early and late stroke-related morbidity and mortality. A delay or lack of proper evaluation of mild cases, including lack of diagnosis because of decreased access to MRI, may have severe consequences such as increased numbers of complications in the early phase of stroke and early stroke recurrence. The risk of recurrent stroke is up to 12.8% in the week after a TIA, with a pooled estimate of 5.2% (95% CI 3.9–6.5) [25]. In the Oxford Vascular Study (OXVASC), early intervention has been associated with an 80% reduction in risk of early recurrent stroke [26].

Further long-term consequences of COVID-19 pandemic have not been analysed so far. Measures of change of mortality due to a disease or to a sudden phenomenon like a hurricane may be only partially due to the direct effect of the cause in the study [27]. In a study considering the excess mortality of the pandemic in USA, only 65% were directly due to COVID-19. Other deaths may have resulted not directly from COVID-19 but connected to worries about possible exposure to SARS-CoV-2 when attending public places and the implementation of the measures favouring the social distancing. The presence of direct and indirect causes of death in the COVID-19 pandemic may determine an underestimation of the total number of deaths and shift the analyses of causes of deaths [28]. This is particularly relevant for stroke in the COVID-19 pandemic. Changes in the general health systems such as reduction of visits of the general practitioners and in the emergency services for non-COVID-19 causes, reduction in the number of beds, reduction in the optimal care of highly prevalent diseases and stroke risk factors such as hypertension and diabetes because of lack of resources in the medical care system, all may determine additional negative impact on the health of the general population.

Hospitalizations in the veteran administration hospitals for emergency conditions including myocardial infarction and stroke have declined by 40% in the first weeks after the onset of pandemic [29]. There have been several reports describing an important reduction of referrals for stroke care. Therefore, there is a range of patients primarily with mild stroke, and perhaps with severe stroke, that do not go to hospitals [30].

It is important to note that an extensive drop in referrals for stroke prevention visits has been reported in the London area in Canada [31]. Considering the differences in race and ethnicity in stroke incidence and risk factors [32,33], it is important to improve our knowledge of the frequency of stroke in various ethnic groups to implement appropriate control methods for COVID-19 in black and Hispanic communities in USA that could increase further preexisting race/ethnicity disparities in stroke care and prognosis [34,35].

The load of possible consequences of this lack of referral needs to be evaluated considering that longitudinal studies are needed to understand the possible consequences of COVID-19 paying special attention to the occurrence of cerebrovascular disease in the acute phase. Furthermore, risk factors or determinants favouring or decreasing the probability that an individual with COVID-19 present cerebrovascular diseases, need to be studied and possibly identified.

The COVID-19 pandemic is a new challenge to the healthcare systems. Stroke, even during the pandemic, is still a time-dependent disease. According to Leira *et al.* [36] and a panel of stroke experts, in this emergency, the healthcare systems for stroke need to be preserved providing at the same time safety measures for health providers and patients. In particular, the fear of contamination and the avoidance of referral paths need to be counteracted through a proper educational campaign on stroke awareness during COVID-19 epidemic in all world. At the same time, the multidisciplinary teamwork and emergency organization characterizing stroke care needs to be preserved even during the emergency [37] (Fig. 2). The use of telemedicine should be appropriately expanded, considering its proven efficacy in stroke care [38–41]. The application of stroke

FIGURE 2. Stroke care at the time of COVID-19 pandemic.

guidelines should be strongly pursued in the era of new global emergencies like the present pandemic.

Epidemiological studies looking for the short and long-term consequences in the area of stroke in the pandemic need to be implemented, also to evaluate the efficacy and the efficiency of possible interventions and new policies.

Acknowledgements

We would like to thank Dr Marco Musio for his assistance with the manuscript.

Financial support and sponsorship

This work was supported by the special grant from Regione Puglia and CNR for Tecnopolo Puglia per la Medicina di Precisione D.G.R. n. 2117 of 21.11.2018.

Conflicts of interest

G.L. and E.B. are Associate Editors of Neuroepidemiology (Karger Publisher).
E.B. reports grants from Italian Ministry of Health, grants from SOBI, personal fees from Arvelle Therapeutics, grants from American ALS Association, all outside the submitted work.
G.L. reports special grant from Regione Puglia and CNR for 'Tecnopolo Puglia per la Medicina di Precisione', all outside the submitted work.

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- ■■ of outstanding interest

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