A statistical analysis of acute ischemic stroke before and during the COVID-19 pandemic

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ABSTRACT

Strokes are very serious neurological disorders, most often with sudden onset, unpredictable evolution and very high mortality. According to the World Health Organization, about 15 million people survive a stroke each year, and 5-6 million die each year from it.

Globally, strokes are one of the leading causes of morbidity and mortality. Relatively recent clinical data show that strokes are the second leading cause of death worldwide. Thus, in Europe, new strokes occur annually in 100-200 cases per 100,000 inhabitants.

For Romania, the epidemiological analysis of the data of our study shows that strokes are the leading cause of death in vascular diseases, i.e. cerebrovascular and cardiovascular diseases put together.

Keywords: acute ischemic stroke (AIS), neuronal death, epidemiology, mortality

INTRODUCTION

Strokes are a major medical and social problem in developed countries as well, being the third leading cause of death after cancer and heart disease and the leading cause of disability [1].

A stroke is a neurological condition characterized by the rapid loss of brain function due to the disruption of the blood supply to the brain. This process can be due to ischemia (lack of blood flow) caused by blocked blood flow due to thrombosis or arterial embolism or caused by a haemorrhage due to the breaking of a blood vessel's wall [2]. As a result, the affected area of the brain cannot function, which could lead to an inability to move one or more limbs on one side of the body, an inability to understand or speak, or an inability to see on one of the sides of the visual field [3].

In 1970, experts from the World Health Organization defined a stroke as a "neurological deficit due to cerebral vascular disease that persists for more than 24 hours or is interrupted by death within 24 hours" [4], although the word "stroke" is centuries old. This definition was to reflect the reversibility of the tissue lesion and was designed for this purpose, with the time interval of 24 hours being chosen arbitrarily. The 24-hour limit separates a stroke from a transient ischemic stroke, which is a syndrome with symptoms similar to a stroke, but which disappears completely within 24 hours [5]. Along with the availability of modern treatments that, when administered early, can reduce the severity of the stroke, many now prefer two concepts, such as **stroke** (for a stroke of more than 24 hours) and **ischemic stroke syndrome**, which reflects the degree of urgency of the stroke symptoms and the necessity of acting quickly [6].

RESULTS

According to the World Health Organization, in 2001 there were 5.5 million deaths from strokes.

Strokes were the third leading cause of death 10 years ago, but since 2008, the incidence of the disease has become the second leading cause of death worldwide, accounting for 6.2 million deaths (approximately 11% of all deaths). In 2013, approximately 10 million people had a stroke and 42.4 million people, who had previously had a stroke, were still alive [7,8]. This clinical-statistical data places strokes in second place, after heart disease, but before cancer [9].

In developed countries, stroke is the third leading cause of death (10) and the most common cause of permanent disability in adults worldwide [11]. After 3 months from the onset of a stroke, between 15-30% of stroke survivors have a permanent disability and 20% require institutional care [12]. Clinical and mental impairments following a stroke may include partial paralysis, memory, thinking, language, and movement difficulties [13,14].

The stroke is also the second leading cause of neuropsychiatric disorders, being considered the leading cause of dementia and the most common cause of epilepsy in the elderly, as well as a common cause of depression [15-17]. According to some authors [18,19], the stroke is the main etiological factor of the onset of long-term disabilities.

There are large geographical differences in the incidence of strokes, more or less explained. In the United States, the stroke is the fifth leading cause of death as a result of medical prevention measures [20].

According to the American Stroke Association (2016), there are about 7,000,000 people over the age of 20 in the United States who have survived a stroke. In the 2000-2015 period, specific mortality from stroke decreased in the US by 3.4%, through severe smoking reduction measures and through a medical activity of raising public awareness about the risks of stroke and the disabilities induced by them, but despite all these measures, the absolute number of deaths increased in the 2013-2015 period by 2.5%/year [21-23].

According to some authors, every 40-45 seconds a person in the United States suffers a stroke. A quarter of the survivors of an initial stroke will suffer a second episode in the next 5 years [24,25].

The incidence and geographical spread of strokes in the United States varies depending on multiple demographic factors such as gender, ethnicity, geographic area and education [26,27]. The eastern states of the United States have been called the "stroke belt" because all states in this area, except Florida, have a rate of 55-65 fatal strokes per 100,000 people.

Ethnic minorities have an increased level of risk for stroke, and African Americans have almost twice as many strokes as whites [28,29]. The incidence rate for Mexicans of American descent is 168 per 100,000 people, compared with 136 per 100,000 for non-Hispanic whites [30].

African Americans of both sexes die in a much larger proportion than white men. Patients with transient strokes (AIT) also have a high mortality rate, up to 25% will die in the first year after the AIT episode [31]. Although the mortality rate in adults aged ≥35 years decreased by 38% from 2000 (118.4 per 100,000 people) to 2015 (73.3 per 100,000 people), strokes remain among the top 5 causes of death, after heart disease, cancer, unintentional injuries, and chronic lower respiratory diseases [21,32].

In Canada, there are about 62,000 strokes a year, of which 60% occur in women, and 16,000 deaths from this cause. There are about 300,000 Canadians who have complications from a stroke [33,34].

In Africa, there has been an alarming increase in strokes in recent decades due to population growth, uncontrolled industrialization and increasing consumption of Western diets, which has led to an alarming increase in several risk factors for vascular disease. Smoking, alcohol consumption, physical inactivity and unhealthy diets have invariably resulted in an increased prevalence of hypertension, diabetes and obesity. According to some estimates, in 2002, in three African countries (Angola, Liberia and Sierra Leone) were recorded the highest rates of stroke mortality in the world [35,36].

Statistics show that in Europe the highest standardized mortality rates are found in Russia, Latvia, Moldova and Romania [37].

At present, in Romania there are a number of approximately 800,000 patients suffering from cerebrovascular diseases.

From this point of view, Romania is in the top ten places in the world in terms of stroke incidence [38].

In a study on the stroke mortality rate in a number of European countries, Romania ranks 3rd, after Bulgaria and Latvia, with mortality values of over 200 per 100,000 for women and over 250 per 100,000 for men. These values are 3 times higher than those recorded in Western European countries [39].

Relatively recent data shows that the prevalence of stroke in Romania is 0.1% for the under 40 years age group, 1.8% for the 40-55 years age group, 4.3% for the 55-70 years age group and 13,9% over the age of 70. No significant differences were noticed between urban and rural areas [40].

The incidence of strokes increases exponentially with age after 30 years [41]. Old age is one of the most significant risk factors for stroke. 95% of strokes occur in people over the age of 45, and two thirds of strokes occur in those over 65 [18]. The risk of stroke death also

increases with age. However, a stroke can occur at any age, including in childhood.

Regarding age, statistical studies show that the maximum incidence of strokes occurs in 75% of cases after the age of 65 [42,43], an age also associated with a much more difficult post-stroke recovery. Post-stroke mortality today is between 20 and 30% [44].

In people over the age of 80, 12.4% of women and 14.8% of men suffered a stroke. The male-female incidence rate is higher than 1.0 for those aged 55 to 84, but decreases to 0.76 in individuals over 85 years of age. Every year, women have 60,000 more strokes than men, which may be associated with their longer lifespan, and this gender gap is growing [45]. Between 1988 and 2004, NHANES (National Health Service and Nutrition Examination Center) studies showed that the rate of attacks tripled among women between the ages of 35 and 54, but remained the same for men in the same age group [46].

The 3-year mortality rate from stroke is 20.7% in women and 22% in men [47].

Although men are 25% more exposed to strokes than women, 60% of deaths in people with strokes occur for women because women live longer [48].

Stroke mortality of any type varies greatly depending on the country, with values between 20 and 250 per 100,000/year [37].

In Romania, there is a death by cerebral infarction or myocardial infarction every 10 minutes [49].

Stroke mortality is three to four times higher than in European Union countries and six to seven times higher than in the United States [50].

This negative statistic does not depend on the economic level of the country, but on the Romanian healthcare system, in which not enough attention is paid to these patients and in which no primary or secondary prevention is done [51,52].

About 15 million people survive a stroke each year, and about 5 million of them remain permanently disabled. Of those who survived a stroke, 10% fully recovered with complete resumption of activities, 40% suffered moderate sequelae with professional reintegration in one-third of cases, 40% had severe sequelae with total or partial disability, and 10% have a total disability and are completely socially dependent. They often have persistent symptoms such as motor deficits, sensory deficits, perceptual, balance deficits, aphasia, depression, dementia or other cognitive function impairments [53,54].

Of the patients who survive a stroke, one third show an improvement in their general condition in the first week of evolution, 40% have a slow evolution, with the appearance of permanent disability, while 20% suffer a worsening of the initial symptoms during the first week of evolution [1].

More than 20% of survivors will need asylum care within 3 months of the event [55].

The social importance of strokes also results from the functional sequelae that develop in stroke patients if they survive [56].

The medical and social costs for treatment, recovery and post-acute care are some of the highest.

Each serious case requires prolonged hospitalization, considerable medicine use and paraclinical investigations.

In the United States alone, medical costs directly or indirectly related to strokes amount to billions of dollars [57].

DISCUSSIONS

In addition to demographic factors, medical conditions and lifestyle have a considerable impact on the patient's level of stroke risk.

The most common causes involved in stroke are hypertension, massive cerebral atherosclerosis, embolism, vascular thrombosis and small vessel occlusion [18].

According to other authors, the most common risk factors involved in the etiopathogenesis of stroke include hypertension, diabetes, smoking, hyperlipidemia and old age [58,59].

Some of the risk conditions associated with strokes, such as high blood pressure, type 2 diabetes, smoking, alcohol abuse, diet, atrial fibrillation, are now curable or can be partially monitored and treated, while others, such as age, sex, race or genetic determinism, evolve independently of any monitoring or treatment [60,61].

Thus, the incidence of stroke is related to age. It doubles for every decade in individuals over 55 years of age. The annual incidence of stroke increases with age [62], from 1:1000 in individuals aged 40-45 years to 20:1000 for 70-85 years.

During a woman's pregnancy, her risk for a stroke increases 2.4-fold [63], and depression increases the risk of a stroke 4.2-fold in patients over 65 [64]. Smokers are twice as likely to have an ischemic attack as non-smokers [65], but the level of risk among those who quit decreases gradually over a 5-year period.

Family members may have a genetic predisposition to stroke or have a lifestyle that contributes to stroke. Higher von Willebrand factor levels are more common among people who have had an ischemic stroke for the first time or have relatives with a stroke [18].

All this data explains why considerable efforts are being made worldwide to get to know the etiopathogenic and morphopathological phenomena that contribute to the occurrence of strokes, as well as the ways to prevent and treat these diseases, as thoroughly as possible.

Cerebral vascular diseases are currently considered one of the most common pathologies and one of the most common causes of morbidity in the world [66]. In recent years, this finding has occurred as a result of the use of medical imaging techniques, such as magnetic resonance imaging (MRI) of the brain, used in the diagnosis and evaluation of patients with cerebral vascular disease. These investigations have shown that, in addition to clinically obvious strokes, characterized by classic symptoms (such as vision issues, language issues, motor issues etc.), there are a much higher number of strokes that do not initially attract attention and which accumulate over time, causing a progressive physical and cognitive deterioration of patients. Therefore, it is imperative that an extremely rigorous clinical examination of patients with minor clinical signs that may have etiopathogenesis in the meningo-cerebral vessels be associated with a brain evaluation using modern imaging, preferably through the efficient use of cerebral magnetic resonance imaging and Doppler ultrasonography, as well as the identification of risk factors, in particular hypertension, heart rhythm disorders, ischemic heart disease, diabetes, dyslipidemia, obesity, smoking, alcohol consumption and a sedentary lifestyle.

A recent systematic review of the scientific literature has confirmed a significant reduction in deaths and the need for institutionalization for patients cared for in neurovascular emergency units, compared to those cared for in regular medical or neurology departments.

While the vast majority of the population considers a stroke to be an emergency that requires immediate medical attention, in reality only up to 50% of patients call emergency medical services in a timely manner. Patients with a suspected stroke should be transported without delay to the nearest medical centre with a neurovascular emergency unit capable of providing emergency treatment. Patients with an onset of symptoms of less than 3 hours should have priority in assessment and transport [67].

During the COVID-19 pandemic, recent studies have shown that SARS-CoV-2 infection may increase acute ischemic stroke risk. In a study by Qureshi [68], a total of 103 (1.3%) patients developed acute ischemic stroke among 8163 patients with COVID-19. Among all patients with COVID-19, the proportion of patients with hypertension, diabetes, hyperlipidemia, atrial fibrillation, and congestive heart failure was significantly higher among those with acute ischemic stroke. In a systematic review and meta-analysis (2021), out of 108,571 patients with COVID-19, acute CVD occurred in 1.4%. The most common manifestation was acute ischemic stroke (87.4%) [69].

In a study that analyzed laboratory-confirmed COVID-19 from 31 hospitals in 4 countries, of the 14.483 laboratory-confirmed patients with COVID-19, 156 (1.1%) were diagnosed with AIS. Sixty-one (39.4%) were female, 84 (67.2%) white, and 88 (61.5%) were between 60 and 79 years of age. The most frequently reported aetiology of AIS was cryptogenic (55/129, 42.6%), which was associated with significantly higher white blood cell count, c-reactive protein, and D-dimer levels than non-cryptogenic AIS patients [70].

Another study result showed a considerable number of young strokes. Although the definition of young stroke is debatable, the majority of the studies considered 50 or 55 years as the cutoff. A percentage of 36% of the AIS patients in our study were <55 years of age and 46% were <65 years of age. These proportions are considerably higher than the population-based reports before the pandemic (12.9%-20.7%). The median age of AIS patients in our study was 68 (58-78) years [71].

A retrospective cohort study conducted between January 20, 2020, and October 1, 2020 showed that ischemic stroke patients with COVID-19 had significantly higher 60-day all-cause mortality compared to propensity score-matched historical controls (ischemic stroke patients without COVID-19) [72]. A multicenter retrospective cohort study of COVID-19 patients with AIS who presented to 30 stroke centers in the USA and Canada between 14 March and 30 August 2020 identified several factors that predict worse outcomes, and these outcomes were more frequent compared with global averages and found that elevated neutrophil-to-lymphocyte ratio, rather than D-dimer, predicted both morbidity and mortality [73].

A systematic literature search, conducted by Tsivgoulis et al., concluded that the younger age of the patients, the absence of known stroke risk factors, the difficulties in weaning from mechanical ventilation, high D-dimer levels, spontaneously prolonged international normalized ratio (INR)/partial thromboplastin time (PTT), multi-territorial acute infarctions, unexpected stroke locations (e.g. splenium of the corpus callosum) should alarm clinicians about the co-existence of stroke and SARS-CoV-2 infection [74].

In the specialty literature, several molecular mechanisms appear to be responsible for the occurrence of ischemic strokes, some possibly associated with COVID-19 infection. Although the pathogenesis of stroke has not been fully elucidated, in the context of COVID-19 it is possible that the affinity of SARS-CoV-2 for ACE2 receptors, which are expressed in endothelial and arterial smooth muscle cells in the brain, allows the virus to affect intracranial arteries, causing the vascular wall to rupture [75]. Therefore, after healing, patients who have gone through COVID-19 need to have their health monitored in order to assess the complications of the SARS-CoV-2 virus infection, thus these people still needing medical supervision.

CONCLUSIONS

It is now well established that strokes are the leading cause of long-term morbidity and disability worldwide, and demographic changes, especially in Europe, with the increasing prevalence of the elderly, have led to an increase in both of the incidence and prevalence of strokes.

Relatively recent statistic clinical data show that strokes are the second leading cause of death worldwide.

Prospective studies show that this condition increases year by year, both in incidence and prevalence, experts from the World Health Organization stating that, by 2030, strokes will become the leading cause of mortality.

The data from our study suggests that strokes are a real health problem worldwide, not only because of the high mortality rate but also because of the consequences on the motor and cognitive performance of survivors. Stroke sequelae can have important effects on the quality of life of the patient and his family.

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REFERENCES

1. Donkor ES. Stroke in the 21st Century: A Snapshot of the Burden, Epidemiology, and Quality of Life. *Stroke Res Treat.* 2018;2018:3238165.
2. Sims NR, Muyderman H. Mitochondria, Oxidative Metabolism and Cell Death in Stroke. *Biochimica et Biophysica Acta* 2009;1802(1):80-91.
3. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. *Lancet.* 2008;371(9624):1612-23.
4. World Health Organisation. Cerebrovascular Disorders (Offset Publications). Geneva: World Health Organization, 1978.
5. Abbott AL, Silvestrini M, Topakian R et al. Optimizing the Definitions of Stroke, Transient Ischemic Attack, and Infarction for Research and Application in Clinical Practice. *Front Neurol.* 2017;8:537.
6. Kidwell CS, Warach S. Acute ischemic cerebrovascular syndrome: diagnostic criteria. *Stroke.* 2003;34(12):2995-8.
7. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2015;386(9995):743-800.
8. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet.* 2016;388(10053):1545-1602.
9. Benjamin EJ, Blaha MJ, Chiuve SE et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation.* 2017;135(10):e146-e603.
10. Hankey GJ. The global and regional burden of stroke. *Lancet Glob Health.* 2013;1(5):e239-40.

11. Feigin VL, Norrving B, Mensah GA. Global Burden of Stroke. *Circ Res.* 2017; 120(3):439-448.
12. Roger VL, Go AS, Lloyd-Jones DM et al. Heart disease and stroke statistics – 2011 update: a report from the American Heart Association. *Circulation* 2011;123:e18-e209.
13. Jenkinson PM, Preston C, Ellis SJ. Unawareness after stroke: a review and practical guide to understanding, assessing, and managing anosognosia for hemiplegia. *J Clin Exp Neuropsychol.* 2011;33(10):1079-93.
14. Douven E, Schievink SH, Verhey FR et al. The Cognition and Affect after Stroke - a Prospective Evaluation of Risks (CASPER) study: rationale and design. *BMC Neurol.* 2016;16:65.
15. Liu S, Yu W, Lü Y. The causes of new-onset epilepsy and seizures in the elderly. *Neuropsychiatr Dis Treat.* 2016;12:1425-1434.
16. Dichgans M, Leys D. Vascular Cognitive Impairment. *Circ Res.* 2017;120(3):573-591.
17. GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2019;18(5):439-458.
18. Boehme AK, Esenwa C, Elkind MS. Stroke Risk Factors, Genetics, and Prevention. *Circ Res.* 2017;120(3):472-495.
19. Katan M, Luft A. Global Burden of Stroke. *Semin Neurol.* 2018;38(2):208-211.
20. George MG, Fischer L, Koroshetz W et al. CDC Grand Rounds: Public Health Strategies to Prevent and Treat Strokes. *MMWR Morb Mortal Wkly Rep.* 2017;66(18):479-481.
21. Yang Q, Tong X, Schieb L et al. Vital Signs: Recent Trends in Stroke Death Rates - United States, 2000-2015. MMWR Morb Mortal Wkly Rep. 2017;66(35):933-939.
22. Centers for Disease Control and Prevention. Underlying Cause of Death, 1999–2018. CDC WONDER Online Database. Atlanta, GA: Centers for Disease Control and Prevention; 2018. Accessed December 14, 2021.

23. Virani SS, Alonso A, Benjamin EJ et al. Heart disease and stroke statistics - 2020 update: a report from the American Heart Association external icon. *Circulation.* 2020;141(9):e139–e596.
24. Singh RJ, Chen S, Ganesh A, Hill MD. Long-term neurological, vascular, and mortality outcomes after stroke. *Int J Stroke.* 2018;13(8):787-796.
25. Benjamin EJ, Muntner P, Alonso A et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation.* 2019;139(10):e56-e528.
26. Jackson SL, Legvold B, Vahratian A et al. Sociodemographic and Geographic Variation in Awareness of Stroke Signs and Symptoms among Adults-United States, 2017. *Morb. Mortal. Wkly. Rep.* 2020;69(44):1617-1621.
27. Howard VJ, Madsen TE, Kleindorfer DO et al. Sex and Race Differences in the Association of Incident Ischemic Stroke With Risk Factors. *JAMA Neurol.* 2019;76(2):179-186.
28. Labarthe DR, Howard G, Safford MM et al; Reasons for Geographic and Racial Differences in Stroke (REGARDS) Investigators. Incidence and Case Fatality at the County Level as Contributors to Geographic Disparities in Stroke Mortality. *Neuroepidemiology.* 2016;47(2):96-102.
29. Keene KL, Hyacinth HI, Bis JC et al; COMPASS, SiGN, and METASTROKE Consortia. Genome-Wide Association Study Meta-Analysis of Stroke in 22 000 Individuals of African Descent Identifies Novel Associations With Stroke. *Stroke.* 2020;51(8):2454-2463.
30. Rodriguez CJ, Allison M, Daviglus ML et al; American Heart Association Council on Epidemiology and Prevention; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Cardiovascular and Stroke Nursing. Status of cardiovascular disease

and stroke in Hispanics/Latinos in the United States: a science advisory from the American Heart Association. *Circulation.* 2014; 130(7):593-625.

31. National Center for Health Statistics. Underlying Cause of Death 1999-2018, Multiple Cause of Death Files, 1999-2018. CDC WONDER Online Database. Atlanta, GA: Centers for Disease Control and Prevention; 2020. Accessed December 16, 2021.

32. Kochanek KD, Xu JQ, Arias E. Mortality in the United States, 2019. NCHS Data Brief, no 395. Hyattsville, MD: National Center for Health Statistics, 2020.

33. Tracking heart disease and stroke in Canada. Ottawa: Public Health Agency of Canada; 2009. Available: www.phac-aspc.gc.ca/ publicat/2009/cvd-avc/pdf/cvd-avs-2009-eng. pdf (accessed 2020 November 21).

34. Musuka TD, Wilton SB, Traboulsi M, Hill MD. Diagnosis and management of acute ischemic stroke: speed is critical. *CMAJ.* 2015;187(12):887-893.

35. Owolabi MO, Akarolo-Anthony S, Akinyemi R et al; Members of the H3Africa Consortium. The burden of stroke in Africa: a glance at the present and a glimpse into the future. *Cardiovasc J Afr.* 2015;26(2 Suppl 1):S27-38.

36. Adeloye D. An estimate of the incidence and prevalence of stroke in Africa: a systematic review and meta-analysis. *PLoS One.* 2014;9(6):e100724.

37. Townsend N, Wilson L, Bhatnagar P et al. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J.* 2016 7;37(42):3232-45.

38. Pavaloiu R, Mogoanta L. Clinical, Epidemiological and Etiopathogenic Study of Ischemic Stroke. *Curr Health Sci J.* 2017;43(3):258-262.

39. OECD/European Union (2018), Health at a Glance: Europe 2018: State of Health in the EU Cycle, OECD Publishing, Paris/European Union, Brussels, https://doi.org/10.1787/ health_glance_eur-2018-en (accessed 2021 December 11).

40. Cinteza M, Pana B, Cocohino E. Prevalence and control of cardio-vascular risk factors in Romania-cardio-zone national study. *MEDICA-a Journal of Clinical Medicine.* 2007;2(4):277-288.

41. Ekker MS, Verhoeven JI, Vaartjes I et al. Stroke incidence in young adults according to age, subtype, sex, and time trends. *Neurology.* 2019; 92(21):e2444-e2454.

42. Avan A, Digaleh H, Di Napoli M et al. Socioeconomic status and stroke incidence, prevalence, mortality, and worldwide burden: an ecological analysis from the Global Burden of Disease Study 2017. *BMC Med.* 2019;17(1):191.

43. Roy-O'Reilly M, McCullough LD. Age and Sex Are Critical Factors in Ischemic Stroke Pathology. *Endocrinology.* 2018;159(8):3120-3131.

44. Fekadu G, Chelkeba L, Melaku T et al. 30-day and 60-day rates and predictors of mortality among adult stroke patients: Prospective cohort study. *Ann Med Surg (Lond).* 2020;53:1-11.

45. Fisher M. Stroke and TIA: epidemiology, risk factors, and the need for early intervention. *Am J Manag Care.* 2008;14(6 Suppl 2):S204-11.

46. Towfighi A, Zheng L, Ovbiagele B. Weight of the obesity epidemic: rising stroke rates among middle-aged women in the United States. *Stroke.* 2010;41(7):1371-5.

47. Scrutinio D, Battista P, Guida P et al. Sex Differences in Long-Term Mortality and Functional Outcome After Rehabilitation in Patients With Severe Stroke. *Front Neurol.* 2020;11:84.

48. Girijala RL, Sohrabji F, Bush RL. Sex differences in stroke: Review of current knowledge and evidence. *Vasc Med.* 2017;22(2):135-145.

49. Ioacara S, Popescu AC, Tenenbaum J et al. Acute Myocardial Infarction Mortality Rates and Trends in Romania between 1994 and 2017. *Int J Environ Res Public Health.* 2019;17(1):285.

50. Ceornodolea AD, Bal R, Severens JL. Epidemiology and Management of Atrial Fibrillation and Stroke: Review of Data from Four European Countries. *Stroke Res Treat.* 2017;2017:8593207.

51. Purcarea VL, Coculescu BI, Coculescu EC. Improving the quality of health care in the Romanian public health system - a priority in the reform process, *Journal of Medicine and Life,* 2015;8(2):166-170.

52. Coculescu BI, Coculescu EC, Purcarea VL. Orientation to the patient as marketing strategy in the Romanian public healthcare system, *Journal of Medicine and Life,* 2016, 9(3): 302-305.

53. Shrivastava SR, Shrivastava PS, Ramasamy JD. Reduction in global burden of stroke in underserved areas. *J Neurosci Rural Pract.* 2013;4(4):475-476.

54. Grefkes C, Fink GR. Recovery from stroke: current concepts and future perspectives. *Neurol Res Pract.* 2020;2:17.

55. de Athayde Costa E Silva A, Viana da Cruz Júnior AT, Cardoso do Nascimento NI et al. Positive Balance Recovery in Ischemic Post-Stroke Patients with Delayed Access to Physical Therapy. *Biomed Res Int.* 2020; 2020:9153174.

56. Ramos-Lima MJM, Brasileiro IC, Lima TL, Braga-Neto P. Quality of life after stroke: impact of clinical and sociodemographic factors. *Clinics (Sao Paulo).* 2018;73:e418.

57. Girotra T, Lekoubou A, Bishu KG, Ovbiagele B. A contemporary and comprehensive analysis of the costs of stroke in the United States. *J Neurol Sci.* 2020;410:116643.

58. Kuriakose D, Xiao Z. Pathophysiology and Treatment of Stroke: Present Status and Future Perspectives. *Int J Mol Sci.* 2020; 21(20):7609.

59. Oza R, Rundell K, Garcellano M. Recurrent Ischemic Stroke: Strategies for Prevention. *Am Fam Physician.* 2017;96(7):436-40.

60. Li RC, Xu WD, Lei YL et al. The risk of stroke and associated risk factors in a health examination population: A cross-sectional study. *Medicine* (Baltimore). 2019; 98(40):e17218.

61. Hankey GJ. Population Impact of Potentially Modifiable Risk Factors for Stroke. *Stroke.* 2020;51(3):719-28.

62. Yousufuddin M, Young N. Aging and ischemic stroke. *Aging* (Albany NY). 2019;11(9):2542-2544.

63. Qureshi AI, Saeed O, Malik AA, Suri MF. Pregnancy in advanced age and the risk of stroke in postmenopausal women: analysis of Women's Health Initiative Study. *Am J Obstet Gynecol.* 2017 Apr;216(4):409. e1-409.e6.

64. Wan-Fei K, Hassan STS, Sann LM et al. Depression, anxiety and quality of life in stroke survivors and their family caregivers: A pilot study using an actor/partner interdependence model. *Electron Physician.* 2017;9(8):4924-4933.

65. Jha P. The hazards of smoking and the benefits of cessation: a critical summation of the epidemiological evidence in high-income countries. *Elife.* 2020;9:e49979.

66. Stocheci CM, Coculescu BI, Coculescu EC. Molecular mechanisms involved in cerebral ischemic-induced neuronal death. *Ro J Med Pract.* 2021;16(4):469-475.

67. Wira CR 3rd, Madsen TE, Chang BP et al; from the Society for Academic Emergency Medicine Neurological Emergencies Interest Group. Is There a Neurologist in the House? A Summary of the Current State of Neurovascular Rotations for Emergency Medicine Residents. *AEM Educ Train.* 2018;2(Suppl Suppl 1):S56-S67.

68. Qureshi AI, Baskett WI, Huang W et al. Acute Ischemic Stroke and COVID-19: An Analysis of 27676 Patients. *Stroke.* 2021;52(3):905-912.

69. Nannoni S, de Groot R, Bell S, Markus HS. Stroke in COVID-19: A systematic review and meta-analysis. *Int J Stroke.* 2021; 16(2):137-149.

70. Ramos-Araque ME, Siegler JE, Ribo M et al; SVIN Multinational Registry and Task Force. Stroke etiologies in patients with COVID-19: the SVIN COVID-19 multinational registry. *BMC Neurol.* 2021;21(1):43.

71. Shahjouei S, Tsivgoulis G, Farahmand G et al. SARS-CoV-2 and Stroke Characteristics: A Report From the Multinational COVID-19 Stroke Study Group. *Stroke.* 2021; 52(5):e117-e130.

72. Harrison SL, Fazio-Eynullayeva E, Lane DA et al. Higher Mortality of Ischaemic Stroke Patients Hospitalized with COVID-19 Compared to Historical Controls. *Cerebrovasc Dis.* 2021;50(3):326-331.

73. Dmytriw AA, Dibas M, Phan K et al. Acute ischaemic stroke associated with SARS-CoV-2 infection in North America, Journal of Neurology, Neurosurgery & Psychiatry. Published Online First: 25 January 2022.

74. Tsivgoulis G, Palaiodimou L, Zand R et al. COVID-19 and cerebrovascular diseases: a comprehensive overview. Ther Adv Neurol *Disord.* 2020;13:1756286420978004.

75. Spence JD, de Freitas GR, Pettigrew LC et al. Mechanisms of Stroke in COVID-19. *Cerebrovasc Dis.* 2020;49(4):451-458.