



The COVID-19 Pandemic, a Risk Management Approach

COVID-19 Pandemisi, Bir Risk Yönetimi Yaklaşımı

① Jacques Reis¹, ② Şerefür Öztürk², ③ Zeliha Tülek³, ④ Peter Spencer⁴

¹Université de Strasbourg, Strasbourg; Association RISE, Oberhausbergen, France

²Selcuk University Faculty of Medicine, Department of Neurology, Konya, Turkey

³Istanbul University-Cerrahpaşa; Florence Nightingale Faculty of Nursing, Istanbul, Turkey

⁴Oregon Health & Science University School of Medicine and Oregon Institute of Occupational Health Sciences, Department of Neurology, Oregon, USA

Abstract

The coronavirus disease-2019 pandemic, one of many global threats to human health, provides an opportunity to analyze how to detect, minimize, and even prevent the spread of future viral zoonotic agents with pandemic potential. Such analysis can utilize existing risk assessment techniques that seek formally to define the hazard, assess the health risk, characterize the health threat, and estimate the probability of occurrence.

Keywords: Brain, SARS, SARS-CoV-2, zoonotic virus, hazard assessment, risk estimation

Öz

İnsan sağlığına yönelik birçok küresel tehditten biri olan koronavirüs hastalığı-2019 pandemisi, pandemik potansiyele sahip gelecekteki viral zoonotik ajanların yayılmasının nasıl tespit edileceğini, en aza nasıl indirileceğini ve hatta yayılmasının nasıl önleneceğini analiz etme fırsatı sunmaktadır. Bu tür analizler, resmi olarak tehlikeyi tanımlamaya, sağlık riskini değerlendirmeye, sağlık tehdidini karakterize etmeye ve bu tehdidin meydana gelme olasılığını tahmin etmeye çalışan mevcut risk değerlendirme tekniklerini kullanabilir.

Anahtar Kelimeler: Beyin, SARS, SARS-CoV-2, zoonotik virüs, tehlike değerlendirmesi, risk tahmini

Introduction

Analyzing the coronavirus disease-2019 (COVID-19) pandemic from a holistic perspective, by combining Environmental Neurology and risk management approaches, could serve to address the major concern of the medico-scientific community: “What went wrong and why?” In other words: “Why are we so unprepared?” (1).

The COVID-19 catastrophe may be compared to disasters caused by non-biological hazards, such as the risk of adverse health effects and premature death from global air contamination (1). Approaches used in risk management may help prepare decision-makers to better cope with future predictable environmental health threats and even with unpredictable hazards. Risk management offers a rational framework to approach and prioritize hazards, whatever their nature (2,3). It allows one to contain the uncertainty

related to the consequences of the occurrence of the hazardous event and thus to envisage various procedures for mitigation and coping. Here, we focus on the first steps of risk assessment; this includes hazard identification, that is description of the nature and source of the environmental agent. Risk characterization addresses health threat, notably in relation to human vulnerabilities. Risk estimation, namely calculation of the probability of occurrence of an event and its consequences, draws on epidemiological and other data.

Risk Analysis

The Hazard

Among the vast estimated number of viruses (1×10^{31}), those that can infect mammals are projected to exceed 300,000 (4,5).

Address for Correspondence/Yazışma Adresi: Jacques Reis, Prof. Conv. Faculté de Médecine, UDS Strasbourg, Strasbourg, France

E-mail: jacques.reis@icloud.com ORCID: orcid.org/0000-0003-1216-4662

Received/Geliş Tarihi: 21.12.2021 **Accepted/Kabul Tarihi:** 23.12.2021

They are found in all environmental milieux (air, water, soil), in living organisms (plants, animals), and their circulation in reservoirs and hosts is heterogenic and largely unknown (5). Of course, only a relatively small number of viruses is known directly to threaten human health, among which are the coronaviruses.

The International Committee on Taxonomy of Viruses created the Coronavirus family in 1975 because, "a large number of corona- and related Nidoviruses were discovered in mammals, birds, insects, fish and reptiles" (6). After 2002, two epidemics boosted research and pointed to the likely role of host-switching bat viruses involved in potentially fatal human diseases, namely Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and Human Coronavirus 229E (HCoV-229E). With the 2019 addition of SARS-CoV-2, the cause of COVID-19, the four coronaviruses appear to have a zoonotic origin (7). In sum, seven coronaviruses are known to infect humans, four of which causing common colds (8). SARS, MERS, HCoV-229E and SARS-CoV-2 are classified as Risk Group 3 (RG3) pathogens according to the World Health Organization (WHO) and the U.S. National Institutes of Health (NIH) (1,9). NIH RG3 members are "Agents that are associated with serious or lethal human disease for which preventive or therapeutic interventions may be available. These agents represent a high risk to an individual but a low risk to the community." NIH RG-4 agents, in which SARS-CoV-2 might be more appropriately classified, are those that pose a high risk both to the individual and the community.

The Exposure

Although each year 16 million humans die from preventable infectious diseases (5), the infectious threat for Humanity is, nowadays, prominently related to zoonotic viruses emerging from wildlife (4,10). Among the great biodiversity of zoonotic viruses, there is an intense "natural" circulation of viruses across reservoirs and among hosts. In Africa and Asia, several tropical ecosystems can shelter such a "virodiversity" (4) and may allow germs to emerge, cross species and thereby trigger human disease outbreaks (11). The emergence of new pathogens remains an issue; three-quarters of emerging pathogens are thought to be zoonotic (12), and most of these are viruses. Wolfe and colleagues propose an interesting approach by addressing two major issues: "What are the sources of our major infectious diseases? Why do so many animal pathogens periodically infect human hosts?" (13). They consider five stages of pathogen transmissibility responsible for non-human epizootic events, limited human disease outbreaks, and endemic human diseases (13). Humans are thought to participate in the emergence of pathogens via their disruption of "natural" ecosystems in association with environmental and demographic factors (14). The spread of microbes (transmission) involves their escape from the host or reservoir of infection (where the infectious agent normally lives and multiplies); transport to the new host; entry into the new host, and escape from the new host to other members of the newly infected species (15,16).

The first step is the animal-to-human transmission of the virus. In the case of COVID 19, this issue is unsolved. How did SARS-CoV-2 escape/jump/spillover to humans? Exposure of humans visiting bat caves in South Asia has been proposed (17). Others have raised the possibility of virus escaping from a research laboratory (18). However, the historical background shows that viral emergences are ever-occurring; the uncertainty lies only in

the questions of when and where. This category of uncertainty is similar to that associated with human life and fate, and hazards can be evaluated in term of risks and probabilities.

Human-to-human transmission is another critical step. SARS-CoV-2 is transmitted in bioaerosols, a route underestimated in the early phase of the pandemic (19). Virus transmission is closely related to human behavior. Person-to-person transmission depends largely on interpersonal proximity, such as crowding (leading to superspreading events) and presence in indoor closed spaces (e.g., ships, hospitals, restaurants, meetings), especially those with poor ventilation systems (1,9). The rate of transmission is based on the reproductive number R_0 , which should be weighted by the dispersion parameter k estimated at 0.1 (involved in the superspreaders description) (20). Omicron, the most recent SARS-CoV-2 mutant, has a U.K. expert-estimated R_0 of 3-5 (similar to that for the polio virus), as compared to the WHO estimate of 1.4-2.4 for the initial strain of the virus and >10 for viruses that cause mumps, chickpox, pertussis and measles (<https://www.vaccinestoday.eu/stories/what-is-r0/>).

Risk Characterization

When a virus has entered/infected a human subject, two possibilities exist: The individual remains asymptomatic or becomes ill. Asymptomatic patients with SARS-CoV-2 are clinically more or less silent even though they may nevertheless spread the virus. Symptomatic patients usually present a benign or mild form of the disease and therefore can be ignored. Few are hospitalized and thus become known to medical authorities. An index case "is the patient in an outbreak, who is first noticed by the health authorities, and who makes them aware that an outbreak might be emerging" (21). The index case is thus unlikely the first to be infected, and several index cases may be recognized in the different populations in which they surface.

For the general population, it is established that a sizeable component of SARS-CoV-2-infected persons is asymptomatic, the percentage varying between 15 and 40% (20,22). Younger people, notably children, are asymptomatic more often than infected adults (22). The ratio for hospitalization of symptomatic patients has ranged from 7% to 14% (23), the variation depending on the methodology employed (connecticut residents-cohort USA versus CDC data). Overall, approximately 90% of SARS-CoV-2 infections are uncomplicated, oligosymptomatic, or cause moderate symptoms not leading to hospitalization (20).

The infection fatality rate (IFR) "the probability of dying for a person who is infected" is around 0.15% which is a lower "average IFR than originally feared" around 3.4% in early Chinese estimations (24,25). This IFR calculation is based on a review of 6 eligible systematic evaluations that combine data from 10 to 338 studies of global spread and IFR, and dates from February 2021 (25). It shows "a substantial global and local heterogeneity" explained notably by "differences in population age structure and case-mix of infected and deceased patients" (25), various exposure of vulnerable age groups (26), as well as the efficacy of the critical care units' treatments. An estimated age-specific IFR has been assessed: it is "very low for children and younger adults (e.g., 0.002% at age 10 and 0.01% at age 25) but increases progressively to 0.4% at age 55, 1.4% at age 65, 4.6% at age 75, and 15% at age 85"(26). Comparable results have been obtained in New York City with a IFR of 14.2% (10.2-18.1) for those aged 75 years and older (27).

Another interesting piece of evidence is "the infection fatality rate is two orders of magnitude greater than the annualized risk of a fatal automobile accident and far more dangerous than seasonal influenza" for middle-aged adults (26). According to a report from the Mayo Clinic in the U.S., about 81% of COVID-19 deaths have occurred in patients aged 65 and older (28).

One of the largest studies of the outcome of COVID-19 was carried out in 218,000 patients hospitalized in France in 2020. Patients with COVID-19 represented 2% of the total number of hospitalized patients across the country. The French official agency's report stated that 46,000 patients required treatment in critical care units, which corresponded to 5% of total hospitalization in these units. Among this population, 82% had at least one comorbidity (e.g., high blood pressure, diabetes, obesity) and 2/3rds had cardiovascular risk factors. The total mortality rate was 20% for COVID-19-hospitalized patients. Risk factors were age (>60 years) and male gender (29). These findings are in agreement with many other studies (20,28,30,31).

Risk Characterization for the Nervous System

The well-known neurotropism of emerging viruses and their ability to cause neurological diseases were estimated in 2005 to range around 49%, even without any reference to SARS (14). The lessons from SARS and MERS, probably because of their limited spread and short illness relative to COVID-19, have not been drawn. However, SARS and MERS also target the human nervous system in the acute phase of illness (32,33), and SARS may trigger long-term complications comparable to those associated with long-COVID (34,35).

The nervous system is involved from the onset of symptomatic COVID-19. Even in patients with mild illness, and at the earliest phase of disease, anosmia and dysgeusia occurred with an estimated prevalence of 34 to 86%, although they were recorded in only 5% of patients in the first Chinese report (33). Early reports suggest that anosmia and dysgeusia are less prominent in cases attributed to the Omicron variant. When hospitalized, up to 74% of COVID-19 patients presented with neurological manifestations, including myalgia, headache, impaired consciousness, stroke, encephalopathies and encephalitis (33). Indeed, neurological complications are leading causes of COVID-19 deaths. Besides specific clinical sequelae of COVID-19, symptomatic patients may complain of post-COVID symptoms, the prevalence of which varies with the length of time following the acute illness. Thus, one study found that 46% of patients were symptomatic after 90 days, as shown in a meta-analysis (36). The prevalent symptoms (fatigue and dyspnea) ranged from 35 to 60% (33). In a French study, up to 70% of post-COVID patients reported neurological symptoms and fatigue (37), and these were associated with altered brain glucose uptake that, in concert with waning symptoms, moderated with time (38).

Risk Management and Mitigation

Several reviews address these concerns from a public health perspective (1,9); here we consider medical issues.

Surveillance of the Hazard and the Exposure Risks

Defining a strategy to prevent the emergence of infectious agents might draw on experience from the surveillance of man-

made production of chemicals. More than 100,000 different chemical compounds were registered and commercialized in the European Union (EU) in year 1981 (39). In 2020, the EU produced 221 million tons of chemicals, including chemicals with known health hazards, such as carcinogenicity, mutagenicity, and reproductive toxicity (40). The EC Inventory Database listed 106,212 unique substances/entries (<https://echa.europa.eu/information-on-chemicals/ec-inventory>) when accessed on December 15, 2021. While the toxic potential of categories of chemicals might be evaluated in experimental systems, regulators never considered the potential biological impact of each compound when the REACH regulation was established (<https://echa.europa.eu/fr/regulations/reach/understanding-reach>). However, should a specific substance approved for use - say in an occupational setting - result in human illness, detailed studies may be undertaken to assess its risk to human health. In a similar vein, Dr. van der Hoek, who discovered the human coronavirus called NL63, in 2003, noted in regard to infective coronaviruses that "hunting begins when a medical doctor flags a disease that appears to be infectious" (41). She states "Searching for unknown viruses is not difficult, but finding new relevant viruses is" (41). Attempts to identify Nature's panoply of germs may therefore have limited value for the purpose of assessing the risk of human infection.

However, with regard to the exposure aspect, and when compared with technological (industrial plants) or other natural hazards (volcanoes), it is interesting to consider specific at-risk areas, which can be circumscribed. Emergence of pathogens occurs more often in specific areas and commonly involves specific human activities and behaviors. For example, the close interaction of humans and live animals in wet markets optimizes the opportunity for pathogen exchange. Creating a specific surveillance of virus host-reservoirs, as well as human activities that increase risk of exposure, as is the practice in occupational medicine, would therefore make sense. Such a sentinel surveillance system exists for several pathogens, such as those causing Lyme disease and Influenza. These provide tools for the early detection of human infection, whatever their clinical condition, symptomatic or not. In September 2021, the European Commission launched Health Emergency Preparedness and Response (HERA) department, the mission of which "is to prevent, detect, and rapidly respond to health emergencies" (https://ec.europa.eu/health/hera/overview_en).

Public Health and Medical Management

This aspect of management addresses the inter-human spread of infection, public health measures designed to minimize community infection (quarantine, isolation, lockdowns, and the closure of borders, schools, universities and workplaces), and the surveillance of hospitalized patients (9,42). After the 2003-2004 SARS epidemic, the Chinese government implemented a passive surveillance system for emerging atypical pneumopathies, China's Pneumonia of Unknown Etiology (43). Unhappily, this tool was activated too late (January 2020) to detect the first human cases of SARS-CoV-2 infection (second half of 2019) (44). Arresting virus spread by containment measures and travel bans was a priority in the early phase of the epidemic, such that by mid-April 2020, COVID-19 deaths plateaued in China in contrast to the experience of most other countries (<https://covid19.who.int/region/wpro/country/cn>). Actually, as shown by mathematical modeling of 288

10). These patients led to undetected clusters and fueled a silent epidemic in the global community (45).

When considering preparedness, education on the nature of contagious diseases, as well as dedicated networks for pandemic management via the World Federation of Neurology, with transnational registries and interactive communication, would be of great interest for our community (46,47,48). Such initiatives have the potential to increase awareness among neurological clinicians and scientists of the neurotropic risk associated with emerging pathogens. In acute and post COVID-19 illness, more than one-third of all signs are related to the brain, and the greatest risk for serious/fatal illness concerns seniors and patients with comorbidities.

Conclusion

The neurological community, which is heavily involved in the management of patients with COVID-19, should improve its awareness and preparedness to face new and novel emerging neurotropic pathogens. New viral pandemics seem to be inevitable, even though the when-and-where are unpredictable. While the COVID-19 pandemic threatens to overwhelm medical institutions, there are other huge chronic environmental risks related to human behavior, including global chemical contamination, global climate change, war, malnutrition, drug use and road traffic accident. Comparison of the various hazards to life would allow humans to create a hierarchical understanding of risk for optimal disease prevention. Risk analysis and management is, in our opinion, the best theoretical framework to address these environmental hazards in a rational way.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: J.R., Ş.Ö., Z.T., P.S., Design: J.R., P.S., Data Collection or Processing: J.R., P.S., Analysis or Interpretation: J.R., Ş.Ö., Z.T., P.S., Literature Search: J.R., Ş.Ö., Z.T., P.S., Writing: J.R., P.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

- Schröder I. COVID-19: A risk assessment perspective. *ACS Chem. Health Saf* 2020;27:160-169.
- Ball D. *Environmental policy health*. McGraw-Hill House. London 2006; p. 283.
- International Risk Governance Council (IRGC). <https://irgc.org/about/>
- Anthony SJ, Epstein JH, Murray KA, et al. A strategy to estimate unknown viral diversity in mammals. *mBio* 2013;4:e00598-e00613.
- Editorial. Microbiology by numbers. *Nat Rev Microbiol* 2011;9:628.
- Ziebuhr J, Preface. *Coronavirus*. Academic Press. *Advances in Virus Research* vol 96. 2016; p. 296.
- Drexler JF, Corman VM, Drosten C. Ecology, evolution and classification of bat coronaviruses in the aftermath of SARS. *Antiviral Res* 2014;101:45-56.
- Hasöksüz M, Kiliç S, Saraç F. Coronaviruses and SARS-COV-2. *Turk J Med Sci* 2020;50(SI-1):549-556.
- Kim DY, Shinde SK, Lone S, Palem RR, Ghodake GS. COVID-19 pandemic: Public health risk assessment and risk mitigation strategies. *J Pers Med* 2021;11:1243.
- Kruse H, Kirkemo AM, Handeland K. Wildlife as source of zoonotic infections. *Emerg Infect Dis* 2004;10:2067-2072.
- Reis J, Spencer PS, Román GC, Buguet A. Environmental neurology in the tropics. *J Neurol Sci* 2021;421:117287.
- Taylor LH, Latham SM, Woolhouse ME. Risk factors for human disease emergence. *Philos Trans R Soc Lond B Biol Sci* 2001;356:983-989.
- Wolfe ND, Dunavan CP, Diamond J. Origins of major human infectious diseases. *Nature* 2007;447:279-283.
- Olival KJ, Daszak P. The ecology of emerging neurotropic viruses. *J Neurovirol* 2005;11:441-446.
- Microbiology Society. Routes of transmission. <https://microbiologysociety.org/why-microbiology-matters/what-is-microbiology/microbes-and-the-human-body/routes-of-transmission.html>
- American Animal Hospital Association. Routes of transmission. <https://www.aaha.org/aaha-guidelines/infection-control-configuration/routes-of-transmission>
- Maxmen A, Mallapaty S. The COVID lab-leak hypothesis: What scientists do and don't know. *Nature* 2021;594:313-315.
- Temmam S, Vongphayloth K, Baquero Salazar E, et al. Coronaviruses with a SARS-CoV-2-like receptor-binding domain allowing ACE2-mediated entry into human cells isolated from bats of Indochinese peninsula. *Research Square* - 17 Sep 2021. preprint. doi: 10.21203/rs.3.rs-871965/v1
- Morawska L, Milton DK. It is time to address airborne transmission of coronavirus disease 2019 (COVID-19). *Clin Infect Dis* 2020;71:2311-2313.
- Salzberger B, Buder F, Lampl B, et al. Epidemiology of SARS-CoV-2. *Infection* 2021;49:233-239.
- Giesecke J. Primary and index cases. *Lancet* 2014;384:2024.
- Institut national de santé publique du Québec. *Revue rapide de la littérature scientifique: Proportion de personnes asymptomatiques, leur réponse immunitaire et leur potentiel de transmission de la COVID-19. Mise à jour le 1er juin 2021, V 4.0.* <https://www.inspq.qc.ca/publications/2989-asymptomatique-transmission-covid19>
- Mahajan S, Caraballo C, Li SX, et al. SARS-CoV-2 infection hospitalization rate and infection fatality rate among the non-congregate population in connecticut. *Am J Med* 2021;134:812-816.e2.
- Ioannidis JPA. Infection fatality rate of COVID-19 inferred from seroprevalence data. *Bull World Health Organ* 2021;99:19-33F.
- Ioannidis JPA. Reconciling estimates of global spread and infection fatality rates of COVID-19: An overview of systematic evaluations. *Eur J Clin Invest* 2021;51:e13554.
- Yang W, Kandula S, Huynh M, et al. Estimating the infection-fatality risk of SARS-CoV-2 in New York City during the spring 2020 pandemic wave: A model-based analysis. *Lancet Infect Dis* 2021;21:203-212.
- Levin AT, Hanage WP, Owusu-Boaitey N, et al. Assessing the age specificity of infection fatality rates for COVID-19: Systematic review, meta-analysis, and public policy implications. *Eur J Epidemiol* 2020;35:1123-1138.
- Mayo Clinic Staff. COVID-19: Who's at higher risk of serious symptoms? <https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/coronavirus-who-is-at-risk/art-20483301>
- Agence technique de l'information sur l'hospitalisation. *Analyse de l'activité hospitalière 2020 – Covid-19. Rapport du 28/10/2021.* <https://www.atih.sante.fr/actualites/analyse-de-l-activite-hospitaliere-2020-covid-19>
- Centers for Disease Control & Prevention. Risk for COVID-19 Infection, Hospitalization, and Death by Age Group. Updated Nov. 22, 2021. <https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html#print>
- Kokturk N, Babayigit C, Kul S, et al. The predictors of COVID-19 mortality in a nationwide cohort of Turkish patients. *Respir Med* 2021;183:106433.
- Arabi YM, Harthi A, Hussein J, et al. Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). *Infection* 2015;43:495-501.
- Maury A, Lyoubi A, Peiffer-Smadja N, de Broucker T, Meppiel E. Neurological manifestations associated with SARS-CoV-2 and other coronaviruses: A narrative review for clinicians. *Rev Neurol (Paris)* 2021;177:51-64.
- Mak IW, Chu CM, Pan PC, Yiu MG, Chan VL. Long-term psychiatric morbidities among SARS survivors. *Gen Hosp Psychiatry* 2009;31:318-326.
- Moldofsky H, Patcai J. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. *BMC Neurol* 2011;11:37.

36. Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, et al. Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. *Eur J Intern Med* 2021;92:55-70.
37. Salmon-Ceron D, Slama D, De Broucker T, et al. Clinical, virological and imaging profile in patients with prolonged forms of COVID-19: A cross-sectional study. *J Infect* 2021;82:e1-e4.
38. Kas A, Soret M, Pyatigorskaya N, et al. The cerebral network of COVID-19-related encephalopathy: a longitudinal voxel-based 18F-FDG-PET study. *Eur J Nucl Med Mol Imaging* 2021;15:1-15.
39. Eurostat. Chemicals production and consumption statistics. *Statistics Explained*. Data extracted in November 2021. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Chemicals_production_and_consumption_statistics
40. Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. *Lancet* 2006;368:2167-2178.
41. King A. How to track down a new virus – and link it to disease, 20 May 2021. <https://ec.europa.eu/research-and-innovation/en/horizon-magazine/qa-how-track-down-new-virus-and-link-it-disease>
42. Talic S, Shah S, Wild H, et al. Effectiveness of public health measures in reducing the incidence of COVID-19, SARS-CoV-2 transmission, and COVID-19 mortality: Systematic review and meta-analysis. *BMJ* 2021;375:e068302.
43. Xiang N, Song Y, Wang Y, et al. Lessons from an active surveillance pilot to assess the pneumonia of unknown etiology surveillance system in China, 2016: The need to increase clinician participation in the detection and reporting of emerging respiratory infectious diseases. *BMC Infect Dis* 2019;19:770.
44. Worobey M. Dissecting the early COVID-19 cases in Wuhan. *Science* 2021;374:1202-1204.
45. Pinotti F, Di Domenico L, Ortega E, et al. Tracing and analysis of 288 early SARS-CoV-2 infections outside China: A modeling study. *PLoS Med* 2020;17:e1003193.
46. Acar T, Acıman Demirel E, Afşar N, et al. The COVID-19 from neurological overview. *Turk J Neurol* 2020;26:58-108.
47. Altunışık E, Arık A. Decreased stroke applications during pandemic: Collateral effects of COVID-19. *Turk J Neurol* 2021;27:171-175.
48. Beghi E, Helbok R, Crean M, et al. The European Academy of Neurology COVID-19 registry (ENERGY): An international instrument for surveillance of neurological complications in patients with COVID-19. *Eur J Neurol* 2021;28:3303-3323.