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Corona Virus Disease 2019 (COVID-19) emerged in December 2019 from Wuhan, China. It typically presents with mild upper respiratory tract infection symptoms and may have life threatening complications, including acute respiratory distress syndrome, acute stroke, myocardial infarction, kidney failure, shock, and even death. Coronavirus infections are known to have neuroinvasive potential with consequent neuropsychiatric manifestations. We analyzed COVID-19 adult patients in the TriNetX database, which is a global health collaborative clinical research platform collecting real-time electronic medical records data from a network of health care organizations (HCOs) from January 20, 2020 to June 10th, 2020. 40,469 patients were diagnosed with COVID-19 among whom 9086 (22.5%) patients had neuropsychiatric manifestations. The most common neurologic manifestations included headache (3.7%) and sleep disorders (3.4%), Encephalopathy (2.3%), Stroke and transient ischemic attack (TIA) (1.0%) and 0.6% had seizures. Most common psychiatric manifestations included anxiety and other related disorders (4.6%), mood disorders (3.8%), while 0.2% patients had suicidal ideation. Early recognition and prompt management of neuropsychiatric manifestations in these patients have a potential to decrease overall morbidity and mortality.

1. Introduction

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS CoV-2) is a highly pathogenic coronavirus identified as causing the novel Corona Virus Disease 2019 (COVID-19). Since its first identification in Wuhan, China in December 2019, the disease has spread at an alarming rate affecting more than five million people in more than 180 countries (CORONA VIRUS, 2020). Although case fatality ratios for COVID-19 may vary amongst various countries, worldwide it has caused over 416,040 deaths (https://coronavirus.jhu.edu) accessed on June 10, 2020, a number much higher compared to its predecessors coronavirus infections such as Severe Acute Respiratory Syndrome Corona Virus (SARS CoV) and Middle Eastern Respiratory Syndrome Corona Virus (MERS CoV), whose combined death toll was less than 2000 (CORONA VIRUS, 2020; WHO, 2003; MERS-CoV, 2020).

Clinical manifestations of COVID-19 are diverse and range from asymptomatic or mild symptoms like fever, headache, myalgia, sore throat, anosmia to the more severe and life-threatening complications that may include pneumonia, Acute Respiratory Distress Syndrome (ARDS), myocarditis, Acute Kidney Injury (AKI), stroke, encephalitis, multi-organ failure, and even death (Avula et al., 2020; Moriguchi et al., 2020). Given the ominously high rate of transmission along with its asymptomatic and atypical presentations, COVID-19 is posing a challenge to health care communities all over the world (Herman et al., 2020). Like any pandemic, to improve the treatment and prevention for COVID-19, it is critical to expand our knowledge about its demographics, transmission pathways, clinical manifestations, and syndromic complexity.

Coronaviruses tend to have neuroinvasive potential which has previously been described for SARS-CoV (Xu et al., 2005; Lau et al., 2004), MERS CoV (Li et al., 2016), HCoV-229E (Talbot et al., 1993), and HCoVOC43 (Dubé et al., 2018). Not surprisingly, similar potential neurotropism for COVID-19 causing a multitude of neuropsychiatric manifestations has been reported (Mao et al., 2020; Helms et al., 2020). In the largest study thus far, Mao et al. reported a case series of 214 admitted patients from Wuhan, China, where approximately one-third of these patients had neurological symptoms including stroke, encephalopathy and myopathy (Mao et al., 2020). A French case series of 58 COVID-19 patients requiring hospitalization found neuropsychiatric manifestations in one-third of patients at the time of discharge (Helms et al., 2020). Other smaller studies have reported possible hypercoagulable state resulting in strokes in COVID-19 patients (Avula et al.,...
However, data is still limited about demographics, severity, frequency and relationship of neurological manifestations with COVID-19 infection. In this study of 40,469 COVID-19 patients, our aim is to describe the demographics, neurological manifestations, and complications of COVID-19, to educate all the frontline healthcare professionals working in these chaotic pandemic times.

2. Methodology

2.1. Data source

De-identified COVID-19 patients’ data was extracted using TriNetX, which is a Global health collaborative clinical research platform collecting real-time electronic medical records data from a network of health care organizations (HCOs). On March 24, 2020, TriNetX fast-tracked updates to its real-world data (RWD) platform to incorporate specific COVID-19 terminology including the diagnosis and the World Health Organization (WHO) and Centers for Disease Control (CDC) specific coding guidelines to support COVID-19 related research. As a result, “COVID-19 Research Network” in TriNetX global network of HCOs represents the largest global COVID-19 dataset.

Data and analysis was done through TriNetX using browser and accessing real-time features on June 10th, 2020. TriNetX does not allow data downloads, or individual patient data for review. However, the TrinetX platform allows analysis in the form of queries. At University of Arkansas for Medical Sciences the data from TriNetX is managed by Arkansas Clinical Data Repository (AR-CDR) maintained by the Department of Biomedical informatics.

2.2. Study protocol

Local IRB deemed this study to be ‘not human subject research’ (global de-identified COVID-19 Research Network data designated for research use), and no IRB approval was needed. Study population included patients with age 18 years or older with a positive diagnosis of COVID-19. For COVID-19 positive diagnosis, we used any event that occurred on or after January 20, 2020 (first reported case of COVID-19 in USA) characterized by one or more of the following ICD-10 diagnosis codes for SARS coronavirus 2: B34.2 coronavirus infection, unspecified; B97.29 other coronavirus as the cause of diseases classified elsewhere (which also includes U07.1 COVID-19; U07.2 COVID-19); J12.81 pneumonia due to SARS-associated coronavirus, and positive laboratory test for 9088 SARS coronavirus 2 and related RNA (presence).

We excluded patients with other coronavirus infections including ICD-9 code 079.89 other specified viral infection. This criteria for accurate identification of COVID-19 has been proposed by TriNetX and has been used in published research.

For COVID-19 patients identified in the TriNetX database, demographic information was analyzed for age, gender, and race and ethnicity. We then identified the subgroup of COVID-19 positive patients for neuropsychiatric manifestations with ICD 10 codes for ‘neurological, psychiatric symptoms and diagnosis’. To identify related diagnosis we have chosen any neuropsychiatric diagnosis on or within one month after diagnosis of COVID-19. These analyses were performed independently by two physicians, with support from a data scientist from Arkansas Clinical Data Repository (AR-CDR).

3. Results

The studied COVID-19 cohort included 22,063 (55%) women and 18,364 (45%) men. A large majority of these patients were in the age group 18–50 years 19,709 (48.7%), while a small but not insignificant group of patients 3830 (9.5%) were above 80 years of age. The racial distribution was: 15,113 (37%) Caucasian, 8350 (21%) African American, 797 (2%) Asian, and 16,000 (40%) of unknown race. Overall, 30,589 (76%) were United States (US) residents and 9880 (24%) were non-US residents. Within the US, regional distribution was 8951 (22%) from the Northeast, 7375 (18%) from the Midwest, 7228 (18%) from the South and 7035 (17%) from the West (Table 1). The COVID-19 cohort included patients from both outpatient 29,830 (73.7%) and inpatient 10,639 (26.3%) settings. Comparative demographic information is presented in Table 1 for Covid-19 patients with neuropsychiatric manifestations.

Of the total 40,469 COVID-19 patients, 9086 (22.5%) patients had neuropsychiatric manifestations. The most common neurologic manifestations included headaches 1501 (3.7%) and sleep disorders 1394 (3.4%). Other manifestations were encephalopathy 937 (2.3%), myalgia 821 (2.0%), pain 723 (1.8%), loss of taste and smell 477 (1.2%), stroke and transient ischemic attack (TIA) 406 (1.0%), dizziness 379 (0.9%), extrapyramidal and movement disorders 277 (0.7%), seizures 258 (0.6%), polyneuropathy 247 (0.6%), and nerve root and plexus disorders 145 (0.4%) (Table 2).

Common psychiatric manifestations included anxiety and other related disorders 1869 (4.6%), mood disorders 1549 (3.8%). Less than 1% of all psychiatric manifestations included emotional state symptoms and signs 318 (0.8%), suicidal ideation 63 (0.2%) (Table 2).

4. Discussion

In this study of 40,469 COVID-19 positive patients, we found 22.5% of patients to have neuropsychiatric manifestations related to COVID-19. This is in accordance with previously reported few small studies (Mao et al., 2020; Helms et al., 2020).

Several proposed mechanisms exist for neuropsychiatric manifestations from COVID-19, which include: direct central nervous system...
Table 2
NeuroPsychological Manifestations.

| Number and Percent of Total Population Studied | n (%) |
|-----------------------------------------------|-------|
| Clinical Observations                         | 9086 (22.5%) |
| Anxiety and other related disorders           | 1869 (4.6) |
| Mood Disorders                                | 1549 (3.8) |
| Headache                                      | 1561 (3.7) |
| Sleep Disorder                                | 1394 (3.4) |
| Encephalopathy                                | 937 (2.3) |
| Myalgia                                       | 821 (2.0) |
| Pain                                          | 723 (1.8) |
| Loss of Taste and Smell                       | 477 (1.2) |
| Stroke and TIA                                | 406 (1.0) |
| Dizziness                                     | 379 (0.9) |
| Emotional State symptoms and signs            | 318 (0.8) |
| Seizure                                       | 258 (0.6) |
| Polyneuropathy                                | 247 (0.6) |
| Extra Pyramidal and Movement Disorder         | 277 (0.7) |
| Nerve Root and Plexus Disorder                | 145 (0.4) |
| Suicidal Ideation                             | 63 (0.2) |

infiltration, cytokine network dysregulation, peripheral immune cell transmigration, and post-infectious autoimmunity etc. (A Review of Pathophysiology and Neuropsychiatric manifestations of COVID-19, 2020; Pérez, 2020; Troyer et al., 2020). Neuroinvasive potential of the coronaviruses and similarities amongst the various coronaviruses’ migration into human host cells have previously been reported (Herman et al., 2020). Gu et al. in 2005 reported that SARS-CoV genome sequences were detectable in the brain of all SARS autopsies, with a preference for hippocampi. Proposed mechanisms of this central nervous system infiltration include direct entry of virus through ACE2 receptors in vascular endothelium from systemic circulation into brain and direct trans-synaptic transfer from the neurons. Similar mechanisms may account for the CNS infiltration of COVID-19 (Yan et al., 2020; Nath, 2020). In our study, 477 (1.2%) patients had symptoms of loss of taste and smell. For COVID-19 patients, neuronal transfer from olfactory bulb through cribriform plate may explain the symptoms of anosmia while viral binding to ACE2 inhibitors in buccal mucosa and tongue may account for ageusia. There were relatively low numbers of patients with loss of smell and taste in our cohort compared to recent reports. This difference might be due to lack of earlier evidence for these symptoms (Tong et al., 2020; Incidence clinical characteristics, 2020). World Health Organization has listed it as a common symptom on April 17th followed by Centers for Disease Control and Prevention. Direct neuronal injury to the cardiorespiratory centers in the brainstem could even be a potential contributing factor to the acute respiratory failure seen in COVID-19 patients.

About 406 (1.0%) patients in our cohort were found to have ischemic stroke and transient ischemic attack (TIA). A recent study from Netherlands showed that 31% of ICU patients with COVID-19 developed various thromboembolic complications (Klok et al., 2020). Cascade of viral binding to ACE2 inhibitors, triggering the inflammatory cytokine release and, and altered coagulation cascade, might be the candidate mechanisms for stroke like symptoms (Avula et al., 2020; Klok et al., 2020; Ounteeddu et al., 2020).

Polyneuropathy along with the nerve root and plexus disorders were seen in about 392 (1.0%) patients in our cohort, which may also be secondary to direct viral invasion precipitating demyelination versus immune mediated damage from inflammatory cytokine surge. There have been reports of Acute Inflammatory Demyelinating Polyneuropathy (AIDP) in the setting of COVID-19 and autoimmune response mediated neural and muscular injury has also been postulated (Wang et al., 2020; Sedaghat and Karimi, 2020; Ottaviani et al., 2019; Scheidl, 2020).

Multi-organ failure is seen in patients with severe COVID-19 leading to hypoxemia, uremia, acidosis and other metabolic derangements. In our study, we have noted several patients with encephalopathy 937 (2.3%), myalgia 821 (2.0%), and pain 723 (1.8%) which can be explained by metabolic abnormalities from multi organ involvement with a possibly contributory role from nervous system involvement by the virus. Headaches 1501 (3.7%) have been found to be the most common neurological symptom in our study which is most likely precipitated by hypoxia and decreased cerebral blood flow. Around 258 (0.6%) of patients had seizures. Decreased seizure threshold from cytokine surge as seen in other viruses might be the underlying mechanism for COVID-19 related seizures.

Our large data set of 40,469 COVID-19 infected patients showed that 1869 (4.6%) suffered from anxiety related disorders, 1549 (3.8%) had mood disorders, 318 (0.8%) had other emotional disturbances and 63 (0.2%) patients had suicidal ideation. Similar to other corona virus epidemics, we anticipated that psychiatric symptoms will not just be isolated to patients affected with COVID-19 but would also involve the health care workers taking care of the patients during the epidemic. Depression, anxiety, mood disorders, and post-traumatic stress disorder (PTSD) were reported amongst frontline healthcare workers during the SARS-CoV-1 epidemic (Lin et al., 2007), MERS CoV outbreak (Lee et al., 2018), and the current SARS-CoV-2 pandemic (Kang et al., 2020; Lai, 2020). In a study of SARS-CoV-1 patient population, Lam et al. reported various psychiatric symptoms including PTSD (54.5%), depression (39%), panic disorder (32.5%), and obsessive compulsive disorder (15.6%) (Lam et al., 2009). Frontline healthcare professionals i.e. those directly providing care to the infected patient population were more prone to report psychiatric symptoms; and amongst this group, nurses and women were found to be most frequently affected (Kang et al., 2020).

A potential strong relationship between coronavirus infections and psychosis seems to exist, and is supported by the observation of increased psychotic episodes in patients with antibodies against four CoV strains versus non-psychiatric controls (Severance et al., 2009) Currently the data for psychiatric symptoms in COVID-19 patients is very limited. In our study, the observed frequency of psychiatric symptoms was lower compared to SARS-CoV-1, which may likely be related to lack of long-term analysis of mental health consequences in COVID-19 patients.

To our knowledge, our study is the largest one, investigating the neuropsychiatric manifestations in COVID-19 positive patients. Our analysis included ICD-10 codes for neurological and psychiatric systems. Despite a large cohort of patients, the current study has several limitations. First, our analysis is based on diagnostic and laboratory results. Despite a large cohort of patients, the current study has several limitations. First, our analysis is based on diagnostic and laboratory codes alone, the individual patient-level data could not be accessed to verify data completeness. Second, this study lacks randomization and confounding factors could not be matched. Third, separate symptom profile analysis could not be done based on race, ethnicity or geographical area. Last, we cannot explicitly establish a strong causal relationship of COVID-19 with the above-mentioned neurological or psychiatric manifestations due to the nature of the study. However, we expect that this study will provide the ground work for future research studies exploring the neuropsychiatric impact of COVID-19 in more detail.

5. Conclusion

Neuropsychiatric manifestations are commonly seen in COVID-19 patients including Anxiety, mood disorders, Headache, Sleep disorders, Encephalopathy, Stroke, Seizures and Neuromuscular complications. Potential mechanisms of neuropsychiatric manifestation include direct CNS infiltration, cytokine network dysregulation, peripheral immune cell transmigration, and post-infectious autoimmune response. Clinicians need to be aware of these manifestations in COVID-19 patients, given the morbidity and mortality of neuropsychiatric involvement. Long term effects of these neuropsychiatric manifestations remains unknown. Early recognition, prompt management, and long term
follow up is warranted to provide better and efficient patient care.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conflicts of interests

Dr. Nalleballe, Dr. Onteddu, Dr. Sharma, Dr. Dandu, Dr Brown, Dr Jasti, Dr. Yadala, Dr. Veerapaneni, Dr. Siddamreddy, Dr. Avula, Dr. Kapoor, Dr. Mudassar and Dr. Kovvuru have no conflicts of interest to report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbi.2020.06.020.

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