Journal of Clinical Neuroscience 91 (2021) 237–242

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Coexistence of neurological diseases with Covid-19 pneumonia during the pandemic period

U. Gorgulu [a,*], H. Bayındır [a,1], H. Bektas [b,2], A.E. Kayipmaz [c,3], İ. San [d,e,4]

[a] Department of Neurology, Ankara City Hospital, Turkey
[b] Department of Neurology, Ankara City Hospital, Ankara Yildirim Beyazit University, Turkey
[c] Department of Emergency Medicine, Ankara City Hospital, Turkey
[d] Ankara City Hospital, University of Health Sciences, Ankara, Turkey
[e] Head of Emergency Health Services, Ministry of Health, Ankara, Turkey

ARTICLE INFO

Article history:
Received 24 January 2021
Accepted 22 June 2021

Keywords:
COVID-19 pneumonia
Neurology
Thorax computed tomography

ABSTRACT

Although clinical findings are related to respiration in the Covid-19 pandemic, the number of patients with neurological symptoms and signs is increasing. The purpose of this study was to assess the prevalence of Covid-19 pneumonia using thoracic CT in patients who presented to the emergency room with neurological complaints during the pandemic. We retrospectively examined the files of 1093 patients who admitted to the emergency room and had a Neurology consultation. The research involved patients who had a neurological diagnosis and had typical findings of COVID-19 pneumonia on thorax computed tomography (CT). The thoracic CT scans of 68 (6.2%) of 1093 patients with neurological disorders at the time of admission revealed results consistent with Covid-19 pneumonia. The "real-time reverse transcription polymerase chain reaction" (RT-PCR) was positive in 42 of the 68 patients (62%), and the patients were diagnosed with Covid-19. Ground glass opacity was the most common finding in thoracic CT in patients diagnosed with Covid-19 pneumonia, with a rate of 92.9% (n = 39). Ischemic stroke (n = 26, 59.5%), cerebral haemorrhage (n = 11, 28.6%), epilepsy (n = 3, 7.1%), transient ischaemic attack (TIA; n = 1, 2.4%), and acute inflammatory demyelinating polyneuropathy (n = 1, 2.4%) were the most common neurological diagnoses among the patients. Even though Covid-19 affects the central and peripheral nervous systems, eliminating the possibility of Covid-19 pneumonia with thorax CT is critical for early treatment and patient prognosis.

1. Introduction

In May 2021, a pandemic caused by a new form of coronavirus (coronavirus disease of 2019, Covid-19) associated to severe acute respiratory syndrome–coronavirus (SARS-CoV-2) resulted in over 160 million confirmed cases and 3 million deaths worldwide [1]. It has been reported that SARS-CoV-2 enters human cells via angiotensin-converting enzyme 2 (ACE2) receptors. The virus first causes interstitial damage in the lungs, followed by parenchymal damage [2]. However, it has been found that the destructive effect of the virus can occur not only in the lungs but also in many systems and organs, including the heart and nervous system. Although ACE2 receptors are found in the nervous system, their presence is not sufficient to explain the nervous system involvement seen in Covid-19 patients, and different hypotheses have been proposed on this issue. These hypotheses are as follows: [1] a neurotropic effect of the virus results in direct invasion into the neurological system; [2] the inflammatory response caused by the virus causes secondary damage to the neurological system; [3] the effects on the respiratory and heart systems result in hypoxemia in the brain; and [4] virus infection and inflammation lead to cerebrovascular disease by affecting the coagulation parameters [3,4].

In a study conducted in the first months of the Covid-19 pandemic in Wuhan, China—the centre of the epidemic—approximately one-third of patients with SARS-CoV-2 infection had

* Corresponding author at: Department of Neurology, Ankara City Hospital Universiteler, Bilkent No: 1, 06800 Cankaya, Ankara, Turkey.
E-mail address: drumitgorgulu@hotmail.com (U. Gorgulu).
[1] Department of Neurology, Ankara City Hospital, Universiteler, Bilkent No: 1, 06800 Cankaya, Ankara, Turkey.
[2] Department of Neurology, Ankara City Hospital, Ankara Yildirim Beyazit University, Universiteler, Bilkent No: 1, 06800 Cankaya, Ankara, Turkey.
[3] Department of Emergency Medicine, Ankara City Hospital, Universiteler, Bilkent No: 1, 06800 Cankaya, Ankara, Turkey.
[4] Ankara Provincial Health Director - Emergency Health Services Presidency, Mehmet Akif Ersoy district, Bagdat Street, No: 62, 06105 Yenimahalle, Ankara, Turkey.

https://doi.org/10.1016/j.jocn.2021.06.041
0967-5868/

symptoms of nervous system involvement (headache, dizziness, loss of taste/smell, etc.) [5]. Furthermore, patients with asymptomatic or paucisymptomatic SARS-CoV-2 infection may develop neurological complications [6]. These findings suggest that patients should be carefully evaluated neurologically. After these evaluations, it was determined that there were many neurological diseases and symptoms, such as meningitis, encephalitis, encephalomyelitis, myelitis, Guillain–Barré Syndrome (GBS) and its variants, muscle diseases and cerebrovascular diseases in patients who had Covid-19 infection during the rapidly progressing pandemic [7].

The collected information shows the importance of evaluating Covid-19 infection in all patients who present to the emergency room or neurology outpatient clinic with neurological complaints and symptoms during the pandemic. This approach is of great importance in terms of preventing late diagnosis or misdiagnosis, as well as protecting healthcare professionals from infection. However, since the symptoms observed during Covid-19 infection are not specific to the disease, rapid and reliable diagnostic tests are required. Although the RT-PCR test for viral nucleic acids is the gold standard in the diagnosis of Covid-19, the sensitivity of the test is only 60%–71% [8]. Problems associated with RT-PCR testing, especially in terms of false-negative results, make the use of thoracic computed tomography (CT) more important for diagnosis [9]. According to studies comparing the sensitivity of thoracic CT and RT-PCR in the diagnosis of Covid-19 illness, the sensitivity of thoracic CT is higher [10,11]. Thus, as the pandemic progresses, thorax CT is playing an important role in faster triage, initial diagnosis and follow-up of patients. In our study, we aimed to evaluate the frequency of Covid-19 pneumonia using thoracic CT in patients who presented to the emergency room with neurological complaints during the pandemic period.

2. Methodology

In our study, we retrospectively evaluated the patient records of 1093 cases who visited the emergency room of Ankara City Hospital and had a neurology consultation between 11 March 2020 and 27 May 2020. This study was approved by the Ethics Committee of Ankara City Hospital (Date: 02/07/2020, Number: E1-20-856).

Because of the delayed results of PCR tests during the pandemic, all patients with respiratory tract infection symptoms in our emergency department were tested with thoracic CT to diagnose pneumonia early, and patients with pneumonia on thoracic CT were isolated before the PCR tests were completed. Patients who were diagnosed with a neurological disease, whose thorax CT findings were compatible with Covid-19 pneumonia and who had positive SARS-CoV-2 RT-PCR results were included in the study. The following data were recorded: demographic data, complaints, comorbidities (hypertension, hyperlipidaemia, coronary artery disease, diabetes, heart failure, atrial fibrillation, chronic renal failure, chronic obstructive pulmonary disease, malignancy, schizophrenia, depression), neurological examination findings, laboratory parameters, thorax CT and brain CT findings, magnetic resonance imaging (MRI) results, hospitalisation diagnoses (stroke, seizure, polyneuropathy), treatments and prognoses of the patients.

The laboratory parameters evaluated in the study were as follows: glucose, urea, creatinine (Cr), albumin, creatine kinase (CK), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), total bilirubin, sodium (Na), potassium (K), calcium (Ca), troponin T/I, B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP), myoglobin, complete blood count (leukocytes, neutrophils, lymphocytes, neutrophils/-lymphocytes, haemoglobin, platelets), prothrombin time (PT), activated partial thromboplastin (APTT), international normalized ratio (INR), fibrinogen, D-dimer, ferritin, the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin, interleukin-6 (IL-6) and SARS-CoV-2 RT-PCR. Cases with negative SARS-CoV-2 RT-PCR results were not included in the study.

Typical (ground-glass opacity, consolidation, reticular pattern, cobblestone appearance [crazy paving], air bronchogram, airway changes, nodules) and atypical (lymphadenopathy, pleural effusion, pericardial effusion, cavitation) findings of Covid-19 pneumonia were evaluated on thoracic CTs of the patients. Cases whose thorax CT findings were not radiologically compatible with Covid-19 were excluded from the study.

Anatomic localisation in cases of ischaemic stroke and cerebral haemorrhage was determined by examining brain CT and MRI imaging results. Ischaemic stroke subtypes were classified as total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), lacunar cerebral infarct (LACI) and posterior circulation infarct (POCI) according to the Bamford classification (Oxfordshire Community Stroke Project). Haemorrhagic stroke cases were classified as intracerebral (putaminocapsular region, hemispheric white matter [lobar], thalamus, cerebellum, basal ganglia, brainstem [mesencephalon, pons, bulbus]) and extracerebral (subarachnoid haemorrhage [SAH], subdural, epidural) according to the anatomic location.

2.1. Statistical analysis

Data were analysed using IBM SPSS software for Windows, version 16. In addition to descriptive statistics (mean, standard deviation, frequency, median, min–max), the chi-square test, one of the non-parametric tests, was used in the evaluation of two independent groups. If the *p*-value obtained as a result of the statistical analysis was less than 0.05, the result was considered statistically significant.

3. Results

The thoracic CT findings of 68 (6.2%) of 1093 patients who visited the emergency room between March 11 and May 27, 2020 and had a neurology consultation as well as neurological diseases at the time of admission were consistent with Covid-19 pneumonia. In 42 of these 68 patients (62%), RT-PCR was positive, and the patients were diagnosed with Covid-19. In our study, the median age of the patients was 73.5 (22–98) years, and the genders were equally distributed (male/female = 1). The patients frequently had comorbidities. In their medical histories, 33.3% ($n = 14$) of the patients had neurological diseases. All the patients were isolated, and 88% ($n = 37$) of them were hospitalised in the intensive care unit, while 1% ($n = 5$) were inwards. The case fatality rate (CFR) was 40.5% ($n = 17$; Table 1).

The complaints at admission were as follows: clouding of consciousness ($n = 13$, 31%), loss of strength in extremities ($n = 12$, 28.6%), speech disorder ($n = 5$, 11.9%), seizure ($n = 3$, 7.1%), walking difficulty ($n = 3$, 7.1%), other complaints (headache, vertigo, syncope, falls, paraesthesia; $n = 6$, 14.3%). Neurological diagnoses of the patients were ischaemic stroke ($n = 26$, 59.5%), cerebral haemorrhage ($n = 11$, 28.6%), epilepsy ($n = 3$, 7.1%), transient ischaemic attack (TIA; $n = 1$, 2.4%) and acute inflammatory demyelinating polyneuropathy ($n = 1$, 2.4%). In 25 patients with ischaemic stroke, 40% ($n = 10$) were categorised as PACI, 24% ($n = 6$) as TACI, 24% (n = 6) as LACI and 12% ($n = 3$) as POCI. In cases of intracerebral haemorrhage, anatomical localisation included 41.7% ($n = 5$) lobar, 16.7% ($n = 2$) basal ganglia, 16.7% ($n = 2$) cerebellum and 25% ($n = 3$) other areas. There was no statistically significant difference (p less than 0.05) in terms of age and gender between ischaemic and haemorrhagic stroke cases.

Table 1
Characteristics of patients with COVID-19 infection.

	n:42	Median (Min-Max)	Unit
Demographic data			
Age	73.5 (22–92)		
Gender	Male 21 (50%) = Female 21 (50%)		
Comorbid disease			
Hypertension	15 (35.7%)		
Coronary artery disease	11 (26,2%)		
Diabetes	9 (21,4%)		
Heart failure	3 (7,1%)		
Atrial fibrillation	2 (4,8%)		
Chronic renal failure	2 (4,8%)		
Chronic obstructive pulmonary disease	2 (4,8%)		
Malignancy	2 (4,8%)		
Hyperlipidemia	1 (2,4%)		
Schizophrenia	1 (2,4%)		
Depression	1 (2,4%)		
Neurological disease	14 (33,3%)		
Stroke	6 (14,3%)		
Dementia	5 (11,9%)		
Parkinson's disease	2 (4,8%)		
Epilepsy	1 (2,4%)		
Reason for consultation			
Clouding of consciousness	13 (31%)		
Loss of strength in extremity	12 (28,6%)		
Speech disorder	5 (11,9%)		
Seizure	3 (7.1%)		
Walking difficulties	3 (7.1%)		
Headache	1 (2,4%)		
Dizziness	1 (2,4%)		
Syncope	1 (2,4%)		
Others (impaired general condition, falls, paresthesia)	3 (7,1%)		
Neurological Disease Diagnosis			
Ischemic Stroke	25 (59,5%)		
TACI	6 (14,3%)		
PACI	10 (23,8%)		
POCI	3 (7,1%)		
LACI	6 (14,3%)		
TIA	1 (2,4%)		
Cerebral hemorroragy	12 (28,6%)		
Lober	5 (41,7%)		
Bazal ganglion	3 (25%)		
Thalamus	1 (8,3%)		
Cerebellum	2 (16,7%)		
Pons	1 (8,3%)		
Epilepsy	3 (7,1%)		
Acute demyelinating polyneuropathy	1 (2,4%)		
Laboratory findings			
LDH	42	332 (63–1746)	U/L
Myoglobin	23	156 (28–1000)	µg/L
Fibrinogen	28	4.48 (0.24–9)	g/L
D-dimer	38	2.4 (0.25–35.2)	mg/L
Procalcitonin	42	0.08 (0.02–4.99)	µg/L
CRP	42	16.5 (0.7–316)	g/L
IL-6	23	124,9 (16.73–1925)	pg/ml
Thorax CT Findings			
Typical			
Ground glass opacity	36 (92,9%)		
Reticular pattern	20 (47,6%)		
Consolidation	15 (35,7%)		
Nodules	6 (14,3%)		
Airway changes	5 (11,9%)		
Air bronchogram	2 (4,8%)		
Cobblestone appearance (crazy paving)	1 (2.4%)		
Atypical			
Lymphadenopathy	2 (4,8%)		
Pleural effusion	4 (9,5%)		
Pericardial effusion	2 (4,8%)		
Prognosis			
Hospitalization in intensive care units	37 (88%)		
Hospitalization in wards	5 (12%)		
CFR	17 (40,5%)		

TACI, total anterior circulation infarct; PACI, partial anterior circulation infarct; PACI, posterior circulation infarct; LACI, lacunar cerebral infarct, TIA, transient ischaemic attack; LDH, lactate dehydrogenase; CRP, C-reactive protein; IL-6, İnterleukin-6; CFR, The Case Fatality Rate.

When the laboratory data were examined, LDH, myoglobulin, fibrinogen, D-dimer, CRP, procalcitonin and IL-6 were found to be high according to the reference values of our hospital. Whereas 92.9% ($n = 39$) of the cases diagnosed with Covid-19 ($n = 42$) had ground-glass opacity in their thorax CT, 47.6% ($n = 20$) had a reticular pattern, 35.7% ($n = 15$) had consolidation, 14.3% ($n = 6$) had nodules and 11.9% ($n = 5$) had airway changes, 4.8% ($n = 2$) had air bronchograms and 2.4% ($n = 1$) had a cobblestone appearance (crazy paving; Table 1).

4. Discussion

As seen in our study and other research aiming to show the coexistence of neurological diseases with Covid-19, neurologists working in emergency rooms during the pandemic process are likely to encounter many neurological diseases, such as stroke (ischaemic or haemorrhagic stroke, TIA), seizure and peripheral neuropathy in Covid-19 patients [7]. In a study of 214 Covid-19 patients, neurological findings were detected in 36.4% of patients; at the same time, neurological findings, including acute stroke, impaired consciousness and muscle damage, were observed more frequently in patients with severe respiratory infections (45.5%) [5]. According to the literature, the high number of patients in our study who required intensive care and CFR (88% vs 32%, 45% vs 2.7%) indicates that the nervous system is more involved in patients with severe infection [1,12]. The high levels of CRP and IL-6 found in our study, as well as LDH, fibrinogen, D-dimer, ferritin, and procalcitonin, are thought to be associated with a poor prognosis [13]. Furthermore, a direct correlation between the prevalence of radiological lesions and the need for intensive care, as well as CFR, has been identified [14]. While the extent of lung involvement in our study was not assessed using thoracic CT, we do know that 92.9% of our patients had ground-glass opacity. It has also been suggested that the virus may affect the respiratory centre, cause disturbances in the cough and gag reflex, or lead to respiratory failure by increasing hypoxia [15].

In Covid-19, cerebrovascular diseases have been reported to be 2–6% in retrospective studies [16,17]. In a study conducted in a neuro-Covid unit in Italy, this rate was reported to be 77% [18]. In our study, stroke was detected in 90% of 42 Covid-19 pneumonia patients with neurological symptoms. Consistent with the literature, most of these patients were over 60 years old and had vascular risk factors [19–24]. It's difficult to interpret the direct association between Covid-19 and stroke because the patients often had other risk factors in the aetiology of stroke, but we can conclude that it raises the risk. Furthermore, Covid-19 infection has been identified as a risk factor for stroke by the Global World Stroke Organization [25].

Neurological findings may be the initial symptoms of Covid-19 in the coexistence of stroke and Covid-19 [26]. That our patients were diagnosed with Covid-19 pneumonia and neurological disease after presenting to the emergency room suggests the neurological presentation of Covid-19. Acute change in consciousness, which was the most common complaint in our study, may be an ischaemic stroke symptom in severe Covid-19 cases [27]. Hypercoagulopathy is the cause of cerebrovascular diseases pathogenesis in Covid-19. It is thought that it can activate inflammatory and thrombotic pathways by causing damage to SARS-CoV-2 endothelial cells [28]. For all these reasons, anticoagulation with low-molecular-weight heparin is recommended to reduce the risk of thrombotic disease in Covid-19 patients [29]. We also found high procalcitonin, CRP, IL-6, ferritin, D-dimer and fibrinogen levels in the patient group with stroke and Covid-19, factors that increase inflammation and hypercoagulability, and we used low-molecular-weight heparin in the treatment.

Cerebral haemorrhage cases in Covid-19 have been limited to isolated cases, and it is not yet clear whether they are coincidental or not [30,31]. In a meta-analysis of 148 Covid-19 patients diagnosed with intracranial cerebral haemorrhage (ICH), in which 23 studies were evaluated, the incidence of ICH was 0.7% [32]. Most of the patients (65.8%) were elderly male patients with comorbidities; the most common comorbid disease was systemic hypertension (54%), and the most common type of haemorrhage was intraparenchymal (lobar) haemorrhage (62.6%). Half of the patients were on some form of anticoagulation [32]. In our study, while haemorrhage was less frequent than ischaemic stroke, it occurred in one-third of the patients hospitalised with a diagnosis of stroke, and it was mostly of the lobar type. Of the 12 patients in this category, whose median age was 77 years, 7 were women. There was at least one vascular risk factor in 83.3% of the patients, and the most common factor was coronary artery atherosclerosis (50%). While three patients were using antiaggregant medications, three were using anticoagulants. Two possible mechanisms of ICH in Covid-19, derived from endothelial injury, are proposed [33]; one is direct endothelial cell invasion, whereas the other is an indirect combination of systemic factors, such as prothrombotic factors, inflammatory cytokine production, activation of coagulation cascades and complement-mediated microvascular thrombosis [34,35]. Regarding the indirect category, there is increasing evidence that Covid-19 infection causes various thrombotic events [36–38]. As a result, disruption of tight junction protein complexes occurs, leading to the blood–brain barrier dysfunction and ICH [34,35]. It is thought that a disruption of the renin-angiotensin system (RAS) may also play a role in Covid-19-mediated ICH. RAS has different regulatory pathways, both in the periphery and in the brain, that can be affected by SARS-CoV-2 through the downregulation of endothelial ACE2 receptors, leading to cerebral blood flow deregulation [39,40].

Whether SARS-CoV-2 virus infection leads to seizure is not yet clear. In general, the findings suggest that seizures and epilepsy are rare, especially in mild cases of Covid-19, but these neurological complications may occur in more severe cases [41]. In our study, the relationship between seizures and Covid-19 was unclear. One of the three cases diagnosed with seizures had a history of epilepsy and stroke. In the other two patients, an intracranial mass and electrolyte disturbance were found, which could explain the seizure aetiology.

One 70-year-old male patient was diagnosed with GBS 6 days after the onset of Covid-19 symptoms. His electromyoneurography was consistent with demyelinating polyneuropathy, and his cerebrospinal fluid examination was free of cells; he had a high protein level and negative results for antiganglioside antibodies. The patient was diagnosed with Covid-19 infection-related GBS and treated with intravenous immunoglobulin. During acute Covid-19 infection, GBS is most common in elderly male patients, and symptoms begin an average of 7 days after the symptoms of Covid-19 infection [42]. Neuro-invasion or autoimmune response of the virus via ACE2 receptors in neuronal tissues is thought to play a role in the aetiology [43,44].

The sensitivity of the RT-PCR test, which is the gold standard in diagnosis for Covid-19, is 60–71%, and a false-negative result may be detected because of laboratory error or insufficient viral material in the sample [8]. In our study, RT-PCR was found to be positive in 62% ($n = 42$) of 68 patients with Covid-19 pneumonia thoracic CT findings. False negativity is more common, especially in the first days, and the result of the RT-PCR test may become positive after 4–8 days [45,46]. However, RT-PCR is time consuming, and because of the shortage of kits, such testing may not meet the needs of an increasingly infected population.

Because of its fast and efficient results in Covid-19 pneumonia, thoracic CT is used in emergency departments, as it was in our research, because early and accurate diagnosis and treatment initiation have an effect on the prognosis. In studies comparing thorax CT and RT-PCR sensitivity in the diagnosis of Covid-19 disease, the sensitivity of thoracic CT was found to be 98% [10,11]. The most common radiological finding in thorax CT is a basal localised, bilateral, peripheral ground-glass image, which is found in 88%–100% of patients [47,48]. In our study, 93% of the patients had a ground-glass appearance on thorax CT. A ground-glass appearance is the first radiological finding of the disease in Covid-19 pneumonia [49]. In a study from China in which 81 cases were evaluated, the authors emphasised that there were abnormalities on thoracic CT even in asymptomatic patients [50]. Thanks to the more widespread recognition of CT findings, various algorithms have been created for the diagnosis of Covid-19 via CT [51]. Furthermore, there are scoring systems that evaluate the severity of the disease using CT, and there are diagnostic studies on Covid-19 pneumonia with artificial intelligence [52,53]. It should be noted that, despite its benefits, tomography is a radiation-based imaging modality that is not a screening method; additionally, thoracic CT had a low rate of missed Covid-19 diagnoses (3.9%). As a result, CT is still limited in its ability to recognise specific viruses and differentiate between them [54,55].

Our research had some limitations. Since our study was retrospective, we did not use scoring systems to determine the severity of the disease. We found no differences in neurological disease severity between Covid-19 (+) and Covid-19 (−) neurological patients. Prospective research is needed and could be beneficial in this regard.

5. Conclusion

Regardless of the presence of respiratory infection findings, it should be kept in mind that Covid-19 may be present in all patients who visit an emergency room with neurological complaints and symptoms during the pandemic. Eliminating the possibility of Covid-19 pneumonia with thorax CT is important for the early treatment and prognosis of patients.

6. Formatting of funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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.

References

[1] WHO Coronavirus Disease (COVID-19) Dashboard: https://covid19.who.int/" HYPERLINK "https://covid19.who.int/%E2%80%9Cs://covid19.who.int [accessed 15 May 2021].
[2] Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci 2020;63:457–60.
[3] Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci 2020;11:995–8.
[4] Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020.
[5] Mao L, Jin H, Wang M, Hu Yu, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77:683. https://doi.org/10.1001/jamaneurol.2020.1127.
[6] Gigli GL, Vogrig A, Nilo A, Fabris M, Biasotto A, Curcio F, et al. HLA and immunological features of SARS-CoV-2-induced Guillain-Barré syndrome. Neurol Sci 2020;41:3391–4.
[7] Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. Lancet Neurol 2020;19:767–83.
[8] Bai H, Hsieh B, Xiong Z, et al. Performance of radiologists in differentiating COVID-19 from viral pneumonia on chest CT. Radiology 2020;296:E46–54.
[9] Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for typical 2019-nCoV pneumonia: relationship to negative RT-PCR testing. Radiology 2020:200343.
[10] Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, et al. Sensitivity of chest CT for COVID-19: comparison to RT-PCR. Radiology 2020;296:E115–7.
[11] A T, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xa L. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: A report of 1014 cases. Radiology. 2020: 200642.
[12] Semagn Mekonnen Abatel, Siraj Ahmed Ali, Bahiru Mantfardo, Bivash Basu. Rate of Intensive Care Unit admission and outcomes among patients with coronavirus: A systematic review and Meta-analysis. 2020 https://doi.org/10.1371/journal.pone.0235653.
[13] Yamanyar S, Yağmurdur H. COVID-19 tanı ve prognozda kullanılan laboratuvar testleri. Yamanel HL, editör. Yoğun Bakım ve COVID-19. 1. Baskı. Ankara: Türkiye Klinikleri; 2020. p. 86-9.
[14] Aydemir Y, Gündüz Y, Köroğlu M, Karabay O, Dheir H, Şengül A, et al. Covid-19'da Radyolojik Tutulumun Yaygınlığı ile Yoğun İhtiyacı ve Mortalitenin İlişkisi. TUSAD SOLUNUM 2020, October 2020. https://www.researchgate.net/publication/344481535.
[15] Duffin J. Functional organization of respiratory neurones: a brief review of current questions and speculations. Exp Physiol 2004;89:517–29.
[16] Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020;19:914.
[17] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavi-rus disease 2019 in Wuhan, China. JAMA Neurol 2020;77:683. https://doi.org/10.1001/jamaneurol.2020.1127.
[18] Benussi A, Pilotto A, Premi E, et al. Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy, Italy. Neurology 2020; published online May 22. https://doi.org/10.1212/WNL.0000000000009848.
[19] Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, et al. COVID-19 presenting as stroke. Brain Behav Immun 2020;87:115–9.
[20] Beyrouti R, Adams ME, Benjamin L, et al. Characteristics of ischaemic stroke associated with COVID-19. J Neurol Neurosurg Psychiatry 2020. published online April 30. doı:jnnp-2020-323586.
[21] Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vasc Neurol 2020;5:279–84. https://doi.org/10.1136/svn-2020-000431.
[22] Morassi M, Bagatto D, Cobelli M, D'Agostini S, Gigli GL, Bnà C, et al. Stroke in patients with SARS-CoV-2 infection: case series. J Neurol 2020;267:2185–92. https://doi.org/10.1007/s00415-020-09885-2.
[23] Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med 2020;382:e38. https://doi.org/10.1056/NEJMc2007575.
[24] Zhai P, Ding Y, Li Y. The impact of COVID-19 on ischemic stroke: a case report. Research Square 2020; published online March 31. https://doi.org/10.21203/rs.3.rs-20393/v1.
[25] Hugh S Markus and Michael Brainin, COVID-19 and stroke—A global World Stroke Organization perspective, Int J Stroke 2020; 15(4) 361–364.
[26] Avulla A, Nalleballe K, Narula N, et al., COVID-19 presenting as stroke, Brain Behav Immunity 2020; 87: 115–119.
[27] Díaz-Pérez C, Ramos C, López-Cruz A, Muñoz Olmedo J, Lázaro González J, De Vega-Ríos E, et al. Acutely altered mental status as the main clinical presentation of multiple strokes in critically ill patients with COVID-19. Neurol Sci 2020;41:2681–4.
[28] Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417–8.
[29] Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020;18:1023–6.
[30] Sharifi-Razavi A, Karimi N, Rouhani N. COVID-19 and intracerebral haemorrhage: causative or coincidental? New Microbe New Infect 2020;35:100669.
[31] Muhammad S, Petridis A, Cornelius JF, Hänggi D. Letter to editor: Severe brain haemorrhage and concomitant COVID-19 Infection: A neurovascular complication of COVID-19. Brain Behav Immun 2020;S0889–1591:30802–3.
[32] Cheruiyot I, Sehmi P, Ominde B, et al. Intracranial hemorrhage in coronavirus disease 2019 (COVID-19) patients. Neurol Sci 2020;3:1–9. https://doi.org/10.1007/s10072-020-04870.
[33] Bengera M, Williamsa O, Siddiquib J, Sztrihaa L. Intracerebral haemorrhage and COVID clinical characteristics from a case series. Brain Behav Immunity 2020;88:940–4.
[34] Ronaldson PT, Davis TP. Mechanisms of endothelial injury and blood-brain barrier dysfunction in stroke. In primer on cerebrovascular diseases: second edition. Elsevier Inc. 2017. p. 220-226 https://doi.org/10.1016/B978-0-12-803058-5.00045-X.
[35] Keep RF et al. (2008) Blood-brain barrier function in intracerebral hemorrhage. In: Zhou LF. et al. (eds) Cerebral Hemorrhage. Acta Neurochirurgica Supplementum, vol 105. Springer, Vienna.
[36] Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145–7.

[37] Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol 2020;S2352-3026:30145–9.
[38] Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. J Am Coll Cardiol 2020;17:27284.
[39] Divani AA, Andalib S, Di Napoli M, Lattanzi S, Hussain MS, Biller J, et al. Coronavirus disease 2019 and stroke: clinical manifestations and pathophysiological insights. J Stroke Cerebrovasc Dis 2020;29:104941.
[40] Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med. 2020;46:586–90.
[41] Hogan RE, Grinspan Z, Axeen E, et al., COVID-19 in patients with seizures and epilepsy: interpretation of relevant knowledge of presenting signs and symptoms. Epilepsy Curr, 1–4.
[42] Kaveh Rahimi. Guillain-Barre syndrome during COVID-19 pandemic: an overview of the reports. Neurol Sci.
[43] Zhou Z, Kang H, Li S, Zhao X. Understanding the neurotropic characteristics of SARS-CoV-2: from neurological manifestations of COVID-19 to potential neurotropic mechanisms. J Neurol 2020;267:2179–84.
[44] Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? Lancet Neurol 2020;19:383–4.
[45] Pan F, Ye T, Sun P. Time course of lung changes on chest CT during recovery from novel coronavirus (COVID-19) pneumonia. Radiology 2020 (Epub ahead of print).
[46] Bernheim A, Mei X, Huang M. Chest CT findings in coronavirus disease-19 (COVID-19): relationship to duration of infection. Radiology 2020 (Epub ahead of print).
[47] Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, et al. Emerging 2019 novel coronavirus (2019-nCoV) pneumonia. Radiology 2020;295:210–7.
[48] Li K, Fang Y, Li W, Pan C, Qin P, Zhong Y, et al. CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). Eur Radiol 2020:1–10. https://doi.org/10.1007/s00330-020-06817-6.
[49] Zhao W, Zhong Z, Xie X, Yu Q, Liu J. Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: a multicenter study. AJR Am J Roentgenol 2020;214:1072–7.
[50] Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020;20:425–34. https://doi.org/10.1016/S1473-3099(20)30086-4.
[51] Nair A, Rodrigues JCL, Hare S, Edey A, Devaraj A, Jacob J, et al. A British Society of Thoracic Imaging statement: considerations in designing local imaging diagnostic algorithms for the COVID-19 pandemic. Clin Radiol 2020;75:329–34. https://doi.org/10.1016/j.crad.2020.03.008.
[52] Yang R, Li X, Liu H, Zhen Y, Zhang X, Xiong Q, et al. Chest CT severity score: an imaging tool for assessing severe COVID-19. Radiol Cardiothorac Imaging 2020;2:e200047.
[53] Ozsahin İ, Sekeroglu B, Musa M.S., et.al. Review on diagnosis of COVID-19 from chest CT images using artificial intelligence. Comput Math Methods Med, 2020. https://doi.org/10.1155/2020/9756518.
[54] Erturk SM. CT of Coronavirus disease (COVID-19) pneumonia: a reference standard is needed. AJR Am J Roentgenol. 2020: W1.
[55] Li Y, Xia L. Coronavirus disease 2019 (COVID-19): role of chest CT in diagnosis and management. AJR 2020;214:1280–6.