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Mayada Elgendy
Mansoura University

Hossam Magdy Balaha
University of Louisville

Mohamed Shehata
University of Louisville

Ahmed Alksas
University of Louisville

Mahitab Ghoneim
Mansoura University, Faculty of Medicine

See next page for additional authors

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Review

Role of Imaging and AI in the Evaluation of COVID-19 Infection: A Comprehensive Survey

Mayada Elgendy[1,†], Hossam Magdy Balaha[2,†], Mohamed Shehata[2], Ahmed Alksas[2], Mahitab Ghoneim[3], Fatma Sherif[3], Ali Mahmoud[2], Ahmed Elgarayhi[1], Fatma Taher[4], Mohammed Sallah[1,5], Mohammed Ghazal[6,‡], Ayman El-Baz[2,*,‡]

[1]Applied Theoretical Physics Research Group, Physics Department, Faculty of Science, Mansoura University, 35516 Mansoura, Egypt
[2]BioImaging Laboratory, Bioengineering Department, University of Louisville, Louisville, KY 40292, USA
[3]Department of Radiology, Faculty of Medicine, Mansoura University, 35516 Mansoura, Egypt
[4]College of Technological Innovation, Zayed University, 19282 Dubai, UAE
[5]Higher Institute of Engineering and Technology, 34517 New Damietta, Egypt
[6]Electrical, Computer, and Biomedical Engineering Department, Abu Dhabi University, 59911 Abu Dhabi, UAE
*Correspondence: aselba01@louisville.edu (Ayman El-Baz)
[†]These authors contributed equally to this work and shared the first authorship.
[‡]These authors share senior authorship.

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Abstract

Coronavirus disease 2019 (COVID-19) is a respiratory illness that started and rapidly became the pandemic of the century, as the number of people infected with it globally exceeded 253.4 million. Since the beginning of the pandemic of COVID-19, over two years have passed. During this hard period, several defies have been coped by the scientific society to know this novel disease, evaluate it, and treat affected patients. All these efforts are done to push back the spread of the virus. This article provides a comprehensive review to learn about the COVID-19 virus and its entry mechanism, its main repercussions on many organs and tissues of the body, identify its symptoms in the short and long terms, in addition to recognize the role of diagnosis imaging in COVID-19. Principally, the quick evolution of active vaccines act an exceptional accomplishment where leaded to decrease rate of death worldwide. However, some hurdels still have to be overcome. Many proof referrers that infection with CoV-19 causes neurological dis function in a substantial ratio of influenced patients, where these symptoms appear severely during the infection and still less is known about the potential long term consequences for the brain, where Loss of smell is a neurological sign and rudimentary symptom of COVID-19. Hence, we review the causes of olfactory bulb dysfunction and Anosmia associated with COVID-19, the latest appropriate therapeutic strategies for the COVID-19 treatment (e.g., the ACE2 strategy and the Ang II receptor), and the tests through the follow-up phases. Additionally, we discuss the long-term complications of the virus and thus the possibility of improving therapeutic strategies. Moreover, the main steps of artificial intelligence that have been used to foretell and early diagnose COVID-19 are presented, where Artificial intelligence, especially machine learning is emerging as an effective approach for diagnostic image analysis with performance in the discriminate diagnosis of injuries of COVID-19 on multiple organs, comparable to that of human practitioners. The followed methodology to prepare the current survey is to search the related work concerning the mentioned topic from different journals, such as Springer, Wiley, and Elsevier. Additionally, different studies have been compared, the results are collected and then reported as shown. The articles are selected based on the year (i.e., the last three years). Also, different keywords were checked (e.g., COVID-19, COVID-19 Treatment, COVID-19 Symptoms, and COVID-19 and Anosmia).

Keywords: artificial intelligence for COVID-19; COVID-19; COVID-19 treatment; COVID-19 symptoms; COVID-19 and anosmia; imaging in COVID-19

1. Introduction

A cluster of fatal pneumonia cases was reported in December 2019. The infection spread rapidly as visitors transmitted the infection to several countries, evoking memories of past pneumonia outbreaks such as Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS). Patients with severe COVID-19 have emerged as a high-risk cohort for invasive fungal infections (IFIs) [1]. Shortness of breath began to spread among patients whose pathological causes were unknown and it was treated as influenza infection at that time [2]. Based on clinical criteria, serologically, and molecular information, the new infection was termed coronavirus disease 2019 (COVID-19) [3]. An increased incidences of cardiovascular has been recognized in those with COVID-19 [4]. Therefore, in the case of patients with cardiovascular disease infected with the COVID-19 virus, it may lead to inflammation of the heart muscle or cardiac arrhythmias and may even lead to death [5]. COVID-19 injuries did not affect the respiratory system only, but also damaged most

of the body's systems in the short and long term, such as the digestive and nervous systems. For COVID-19, there is an elevated rate of cerebral outcomes, especially Anosmia caused by the effect of COVID-19 on the olfactory bulb. Loss of smell is an early sign of infection, which can take weeks, months, or more (i.e., up to a year to recover from) [6]. The number of infections and deaths from COVID-19 has increased worldwide. However, the number of people healing from COVID-19 infection has increased. Statistically, for November 13, 2021, the number of COVID-19 cases worldwide has reached nearly 253.4 million, the total number of deaths worldwide is about 5.1 million, and the total number of people recovered worldwide is about 229.2 million. The total number of COVID-19 patients per million of the world's population is about 32,506, while the total number of COVID-19 deaths per million of the world's population is about 655.3 [7].

1.1 Survey Objectives and Contributions

The main objective of the current survey is to review to learn about the Role of Imaging and AI in the Evaluation of COVID-19 Infection. This is done by gathering knowledge about COVID-19 virus, its main repercussions on many organs and tissues of the body, to identify the symptoms of COVID-19 in the short and long term, as well as the post-acute consequences of COVID-19 infection on many organs of the body. Additionally, this work reviews the causes of dysfunction and loss of sense of smell associated with COVID-19, the latest appropriate therapeutic strategies to combat COVID-19, and methods of follow-up for those recovering from COVID-19. It discusses the long-term complications of the virus and thus the possibility of improving therapeutic strategies. Also, the main steps of artificial intelligence that are used to predict and early diagnose COVID-19 are presented. The contributions can be summarized in points as follows:

– Reporting the COVID-19 infection and its entry mechanism.

– Presenting the early common impacts and symptoms of COVID-19 in the short-term and discussing the impacts and symptoms of COVID-19 in the long-term.

– Discussing the impacts of COVID-19 on the olfactory bulb which lead to Anosmia.

– Presenting the diagnoses imaging In COVID-19 and its outcomes.

– Presenting the treatment strategies and follow-ups.

Getting familiar with the COVID-19 AI systems' internals and reviewing state-of-the-art published articles concerning the different AI-based system phases.

1.2 Paper Organization

The current survey is organized as follows: the following section presents the COVID-19 infection and its Entry Mechanism. Section 2 discusses early common impacts and symptoms of COVID-19 on both short-term and long-term. It discusses the impacts of COVID-19 on the olfactory Bulb which can lead to Anosmia. Additionally, the diagnoses imaging in COVID-19 and its outcomes is presented. Section 3 presents the treatment strategies and follow-up approaches. Section 4 concerns the AI-based systems related to COVID-19 and their phases, in addition to comparing different state-of-the-art published studies. The limitations of the current survey are presented in Section 5. The survey is concluded and the future work is discussed in Section 6.

2. COVID-19 Infection and COVID-19 Virus Entry Mechanism

The current section briefly provides a definition of COVID-19, the type of viruses to which COVID-19 belongs, and the similarities of it with previous coronaviruses. SARS-CoV-2 acts as the 7th member of the Coronaviridae family recognized to infect humans. Its analogs contain four families of weak effects (229E, OC43, NL63, and HKU1), in addition, to two other B-coronaviruses that caused the prior spread of acute and potentially lethal respiratory tract infections—SARS-CoV and the Middle East respiratory syndrome- Coronavirus (MERS-CoV) [8]. Coronavirinae (i.e., coronavirus) is a subfamily of viruses that infect mammals, often presenting as respiratory or enteric infections. Coronaviruses are large, positive, single-strand RNA viruses. Their morphology can be described as spherical virions with a central shell and surface protrusions like the solar corona as shown in Fig. 1 [9]. SARS-CoV-2 is closely related to the SARS-CoV virus [9]. It also participates in the same cellular receptor as SARS-CoV which is the angiotensin-converting enzyme 2 (ACE2) receptor [10]. ACE2 receptors are reinforced in alveolar epithelial type II cells of lung tissues [11], as well as extrapulmonary tissues such as the heart, endothelium, renal, and intestines [12,13], which might play a role in the multi-organ impacts of COVID-19. SARS-CoV-2 has the typical characteristics of coronaviruses. It contains a genetic sequence of 79% identical to SARS-CoV and 50% related to the MERS-coronavirus (MERS-CoV) [14,15]. The severity of COVID-19 infection ranges from very mild to severe as the levels of infection severity depend on the individual's immune system, age, and comorbidities [16].

2.1 COVID-19 Virus Entry Mechanism

Entry of virus into host cells is a prerequisite for coronavirus infection. Spike protein (S protein) interacts with the receptors of host cells, hence, it causes the fusion of the membranes of the cellular and viral. Via biological analysis, the S protein of both COVID-19 and SARS-CoV is similar. To infect epithelial cells, the S protein interacts with the ACE2 receptor on the surface of host cells [17]. So, the ACE2 molecule is the primary molecule of COVID-19 infection [17]. ACE2 is expressed in the human respiratory system as well as in arterial endothelial and smooth muscle cells. It has a crucial and major role in the COVID-19 in-

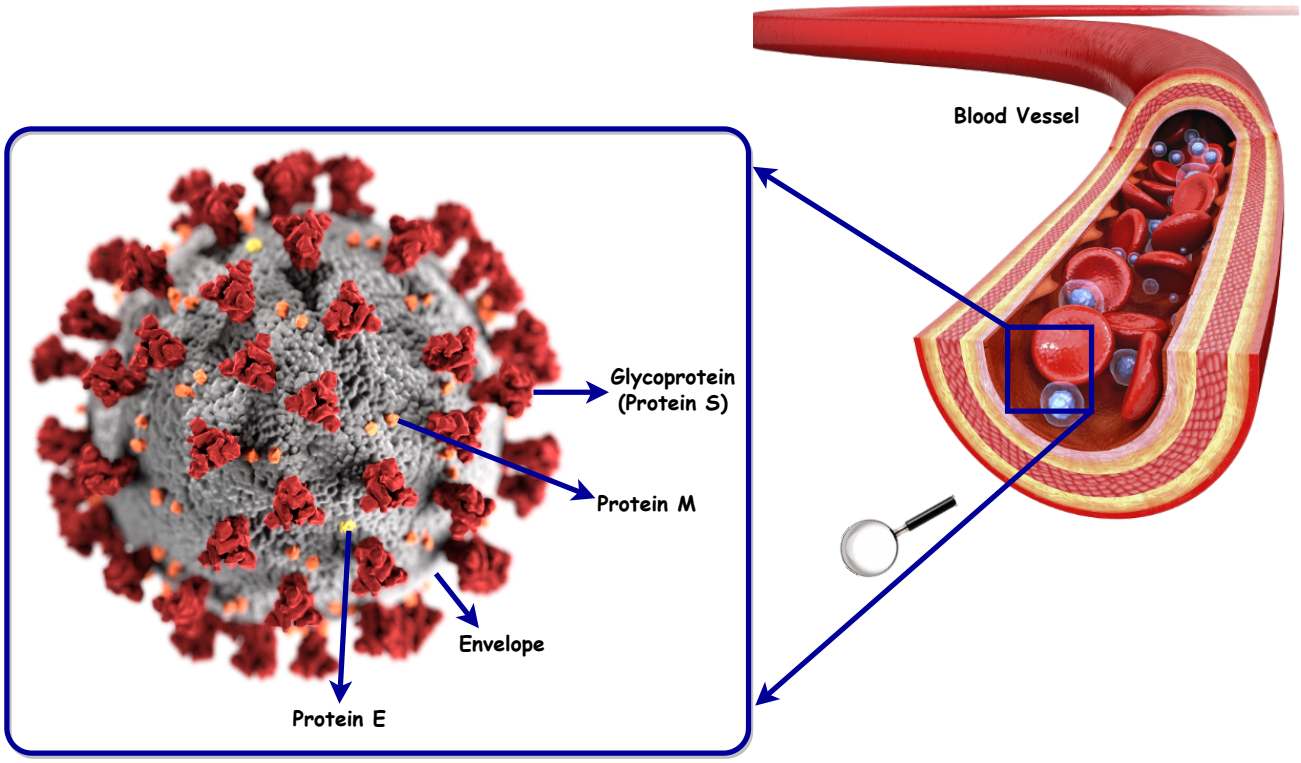

Fig. 1. The Coronavirus Morphology.

fection [13]. Transmission of infection occurs through three possibilities: transmission of respiratory droplets by coughing or sneezing, aerosols, usually during clinical transactions to produce aerosols, and mucosal link with fomites [18,19].

2.2 Early Common Impacts and Symptoms of COVID-19 on Short-Term

The current subsection presents the main clinical symptoms of COVID-19 infection in the short term. Pneumonia is the early medical diagnosis of the SARS-CoV-2 [16]. The clinical symptoms include fever, cough, nasal congestion, and fatigue, in addition to other signs such as shortness of breath [9]. The most common signs of viral pneumonia are low oxygen levels and blood gas aberrations. Also, ground-glass opacity, irregular fusion, alveolar exudation, and interlobular involvement are the most common signs of pneumonia in medical images [20]. Francone *et al*. [21] investigated the short-term impact of COVID-19. Their study used computed tomography (CT) to determine its predictive ability to patient outcomes. Then, a correlation between a semi-quantitative result of pulmonary embroilment in pneumonia resulting from COVID-19 with clinical progression and laboratory outcomes was computed. The study included 130 COVID-19 patients, and all of them experienced an RT-PCR test to confirm their infection. The most common clinical appearance was fever, coughing, dyspnea, and high temperature. The raised levels of CRP existed in 86% patients and raised levels of D-dimer existed in 87.7% patients. Reduced lymphocyte number was observed in 61.5% patients, reduced O2 saturation was observed in 40.1%, and reduced PaO2/FiO2 ratio was observed in 66.2% patients. According to Chinese CDC clinical results [22], 60.8% were categorized as mild, 32.3% as severe, and 6.9% as serious. Concerning the beginning time of symptoms, cases were classified as either early (i.e., 0–7 days) or late clinical manifestations (i.e., >7 days) [23]. The study also proved the following: the early stage (7 days after symptoms appear) of COVID-19 infection is characterized by the spread of ground-glass opacity. The late stage of infection was characterized by a crazy-paving pattern, consolidation, and fibrosis. In severe COVID-19 cases, CT scans give very good and clear results compared to simple COVID-19 cases. In late-stage COVID-19 infection, the CT findings correlated with d-dimer and C-reactive protein (CRP) levels [16]. Neurological manifestations range from minor symptoms such as loss of smell, dizziness, and headache to severe symptoms such as seizures and encephalitis [24]. Fig. 2 summarizes the COVID-19 symptoms on short-term. Although anosmia belongs to the early symptoms of infection in short term, recovery from it may extend for months or more, and therefore it also falls within the long-term effects of COVID-19.

2.3 Common Impacts and Symptoms of COVID-19 on Long-Term

The COVID-19 pandemic presents a direct unprecedented and still identifies as a threat, especially to health

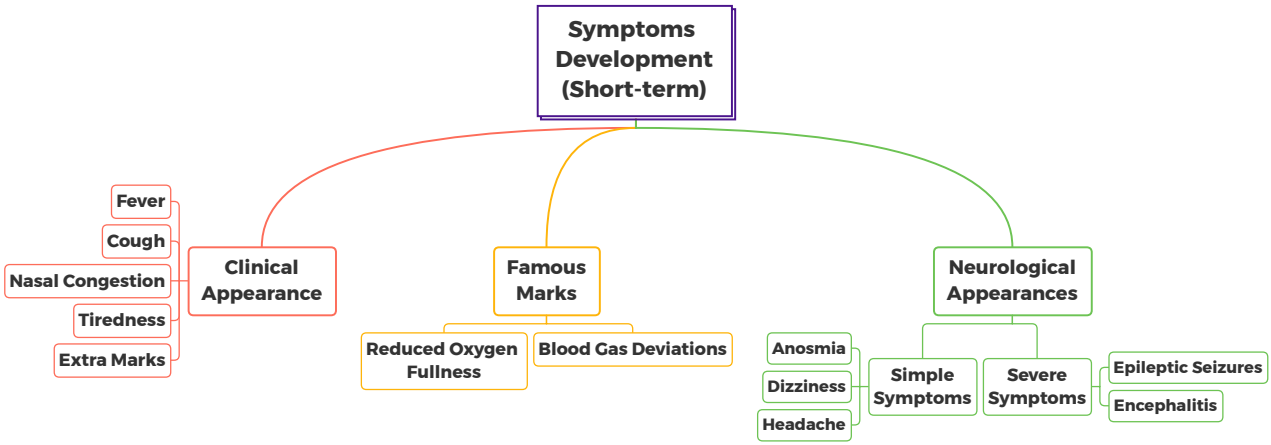

Fig. 2. Short-term symptoms development summarization.

care systems. Worldwide, the total number of infected patients skipped the health care system capacities, especially the patients that needing helped ventilation. During the severe stage of COVID-19 infection, nearly 36% of cases develop neurological symptoms, 25% of which can be attributed to the immediate involvement of the central nervous system. For example, the major symptoms contain headache, dizziness, seizure, and impaired consciousness [25]. Among patients presenting with neurological symptoms, there may be cases with (or without) pre-existing neurological disorders [26]. Affected people displayed excitation, chaos, and corticospinal tract signs, e.g., enhanced tendon reflexes and clonus during intensive care units, while in mild to intermediate disease cases about 85.6% of patients reported olfactory dysfunctions and about 88.0% of patients reported gustatory dysfunctions. Interestingly, around 11% of patients reported anosmia occurred first before any other symptoms [27].

Additionally, COVID-19 can cause alterations in coagulation, especially inflammation-produced disseminated intravascular coagulation (DIC). DIC can lead to cerebrovascular ischemia including the little patients, jointly with endothelial dysfunction, where several of them suffer from big vessel ischemic stroke [28]. About 5.7% of the acute cases experienced ischemic stroke [25] or had preexisting vascular hazard agents particularly in the old person, in whom ischemic stroke rather occurred as a delayed complication [29,30]. Further, sub-acute symptoms that occurred 3–10 days after the evolution of COVID-19 symptoms such as Guillain-Barre´ syndrome [31] and Miller-Fisher syndrome [32]. The adverse effect of COVID-19 on the central nervous system is expressed by several possible mechanisms such as direct viral encephalitis, systemic inflammation, dysfunction of peripheral organs (i.e., liver, kidney, lung), and cerebrovascular alterations. However, many cases may show a mixture of these neurological appearances [26]. In addition to neurological damages, acute renal injury, hyperglycemia, thrombotic problems, cardiac dysfunction, arrhythmia, acute coronary syndromes, and hepatocyte injury are other symptoms of COVID-19 [33,34]. Persons who survive COVID-19 may be at risk of developing long-term neurological consequences due to aggravating a pre-existing neurological disorder or by emerging a new disorder [26]. The presence of COVID-19 infection is linked with an acute immune response and increased levels of systemic cytokines. Accordingly, this innate immune response has been exploited to predict infection severity and mortalities rate [35]. Cytokines and inflammatory mediators that have raised levels in response to COVID-19 infection include: interleukin-1β, interleukin-2, interleukin-2 receptor, interleukin-4, interleukin-10, interleukin-18, interferon-γ, C-reactive protein, granulocyte colony stimulating factor, CXCL10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α [36,37]. In addition to this, T-cell depletion in many COVID-19 patients and reduced lymphocyte number are considered signs [38,39]. In parallel, acute respiratory distress syndrome (ARDS) is the most prevalent clinical presentation among COVID-19 patients [40], as lung injury models in mice and some ARDS patients confirmed the role of NLRP3 in the pathogenesis of infection with acute respiratory distress syndrome and negative results [41,42]. Also, the inflammatory activity of NLRP3 is stimulated by the coronavirus ORF3a protein [43]. In addition, ventilation-produced hypercapnia has been experimentally shown to lead to cognitive impairment in a NLRP3 inflammasome-interleukin-1β-dependent manner [44]. The long-term impact of COVID-19 on other organs such as:

– **Blood**: The number of patients who experienced thromboembpost-acute COVID-19 is less than 5%, and the period for COVID-19 hyperinflammation is unknown. Anticoagulants and low molecular weight heparin are considered long-term anticoagulant prophylaxis in persons at risk of persistently elevated d-dimer levels, loss of motility, or high-risk comorbidities [45].

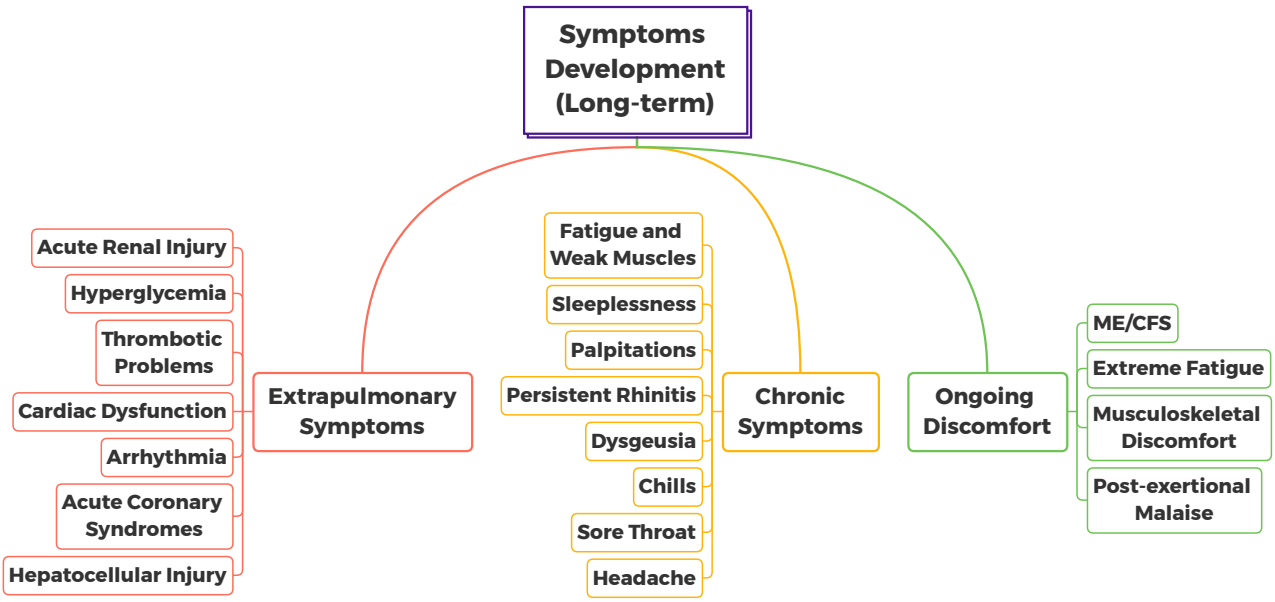

Fig. 3. Long-term symptoms development summarization.

– **Kidneys**: Most patients recover from acute kidney injury during the follow-up interval, however, during 6 months of follow-up, a decrease in the estimated glomerular filtration rate (eGFR) was reported. COVID-19-associated nephropathy (COVAN) is most commonly found among people of African descent, among those who suffer from chronic problems in kidney function and recover from COVID-19. Early follow-up for these patients in the clinics specializing in acute renal impairment is necessary [45].

– **Endocrine**: Endocrine sequelae include new or worsening control of diabetes mellitus and moderate thyroiditis. In cases of newly diagnosed diabetes, in the absence of conventional risk factors for type 2 diabetes, laboratory tests for hypothalamic-pituitary-adrenal axis suppression or hyperthyroidism should be performed and the patients should be referred to an endocrinologist [45].

– **Hepatobiliary and Gastrointestinal**: Even after a negative result on nasopharyngeal swab examination, a prolonged viral signal may be detected in feces following COVID-19 infection. By fertilizing opportunistic organisms and reducing beneficial compensation, COVID-19 can change the gut microbiome [45].

– **Dermatologic**: Hair loss is a common symptom, with around 20% of PASC patients reporting it [45].

– **Multisystem Inflammatory Syndrome in Children (MIS-C)**: MIS-C is also known as a pediatric multisystem inflammatory syndrome. According to the WHO, fever, severe inflammatory signs, and multiple organ dysfunction are most common among people under the age of 21. Children's injuries occur in those whose ages are under 7 years. Cardiovascular and neurological disease, fever, abdominal pain, vomiting, diarrhea, and rash are the clinical manifestations of MIS-C [45].

COVID-19 infection often lasts between one to four weeks [46]. However, a subset of patients who become infected with SARS-CoV-2 develop a variety of chronic symptoms that last for months [46,47]. Nearly 30% of COVID-19 patients, who were followed up for 9 months, had chronic symptoms. Post-acute sequelae of COVID-19 (PASC) is the most appropriate term to describe the issues faced by these patients [48]. Fig. 3 summarizes the COVID-19 symptoms on long-term.

2.4 Impacts of COVID-19 on Olfactory Bulb which Lead to Anosmia

The current subsection presents the relationship between COVID-19 and partial (or complete) Anosmia. The olfactory nerve is described as being tiny in size and can only be seen by MRI of the base of the skull [49]. The olfactory bulbs are located over the cerebral plate, below the olfactory sulcus, and inside the anterior cranial fossa [50] as shown in Fig. 4. The morphology of the olfactory bulb was considered normal if it appeared in an oval shape or J shape and abnormal if it appeared in an oblong or atrophic appearance [51]. Reverse neurological signs have been recognized in the configuration of hyposmia, anosmia, headache, dysgeusia, disgust, puke, commotion, raving, and wreaked realization [52–56].

Coronaviruses are mostly neurotropic [57], where the particles of COVID-19 were revealed in human brain neurons [12]. Therefore, CoV-19 can arrive in the CNS, hence, causing neuronal damage. There are three suppositions of CoV-19 entrance into the CNS, namely, intranasal inoculation with diffusion by the olfactory bulb and nerves to the brainstem, transsynaptic diffusion from neuron to neuron by endocytosis (exocytosis), or hematogenous diffusion

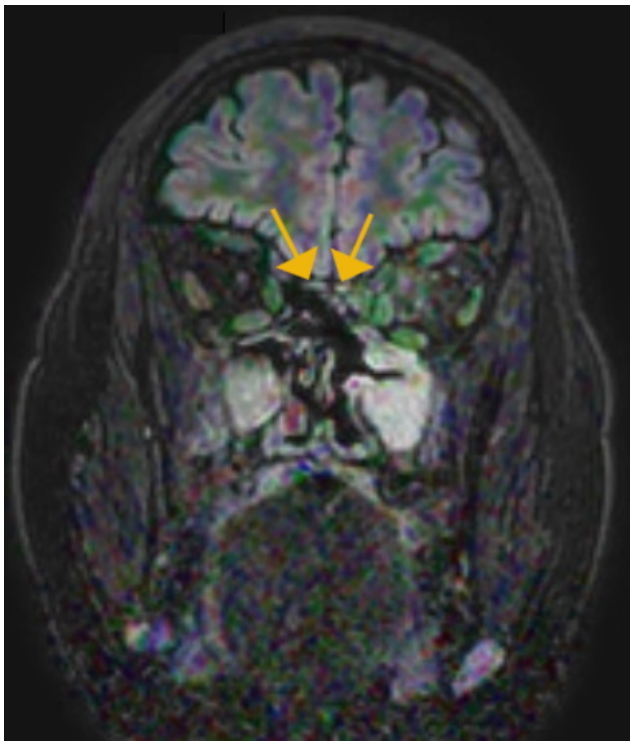

Fig. 4. The location of the olfactory bulbs in a DTI image for a COVID-19 patient.

by affected monocytes and crossing the blood-brain barrier [58]. There are three mechanisms for Pathophysiology of CNS from COVID-19, either immediate viral entrance into the brain, inverse immune response, or respiratory strain [59]. Recently, the empirical proof showed that a human CoV progeny and HCoV OC43 can be transported to the olfactory bulb through the nasal cavity, then diffuse to the piriform cortex, and brainstem by the negative outbreak and axonal transition [60,61]. There are a large number of viruses that interact with the receptors of the nasal mucosa, resulting in inflammation-causing the dysfunction [62]. The upper respiratory tract does not have distinct symptoms that enable the doctors to differentiate with certainty between infection with COVID-19 and other viruses. As the mechanism of viral infection for most viruses is similar, the virus enters through the epithelium of the respiratory tract and interacts with the ACE2 receptors [63]. The interaction may occur directly or indirectly, thus, the olfactory neurons may be affected and lead to the emergence of neurological symptoms [64].

Strauss *et al*. [50] proved that the MRI is a reliable medical imaging method to confirm olfactory system injuries in those who suffer from COVID-19 with the presence of neurological symptoms. The diseases of the olfactory bulb in people with COVID-19 are a defect or anomalies in the olfactory bulb signal. Chiu *et al*. [49] have noted that the loss or decreased sense of smell is one of the symptoms of COVID-19, as 60% of people with COVID suffered from it. However, the olfactory nerve was not primarily scanned. This study examined 19-year-old female suffering from persistent loss of smell as a result of COVID-19 infection. The patient underwent RT-PCR to confirm the infection and the result was positive. After recovering from the infection, she still suffers from anosmia. An MRI was performed after two months to find out that atrophy in the olfactory bulb is the reason for the continued loss of smell. By comparing the result of the MRI that the patient had previously done for other reasons and the current imaging due to infection with COVID-19, it was proved that there was a difference in the sizes of the olfactory bulbs. The size of the olfactory bulb 3 years before the loss of smell due to COVID-19 was 47.46 mm^3 and 49.5 mm^3, The size after the loss of smell was 35.51 mm^3 and 29.96 mm^3 while the minimum size of the olfactory bulb for women under the age of 45 is 54 mm^3.

2.5 Diagnosis Imaging in COVID-19 and Its Outcomes

Medical imaging techniques play a major part in diagnosing the infection with COVID-19, primely, concerning the first symptoms of pulmonary disease and the tissue allocation of the angiotensin-converting enzyme 2 (ACE 2) receptor. The non-sensitivity of RT-PCR scans for positive diagnosis is the main motive for resorting to medical imaging approaches.

Quantitative imaging including the "radiomics and artificial intelligence" introduced interesting findings in pulmonary disease detection in the short- and middle-term and foretell long-lasting fibrotic alters [65,66]. In extension to the different pulmonary symptoms, COVID-19 is a systemic disease with broad impacts on matures and youths that can be evaluated using imaging [67–70]. For example, Gastrointestinal symptoms, colitis signs at computed tomography such as bowel wall thickening [68–71], olfactory bulb abnormality in MR and induced anosmia [51,69]. Additionally, myocarditis-similar markers such as myocardial edema or delayed gadolinium enhancement in children who are suffering from multisystem inflammatory syndrome (MIS-C) due to COVID-19 [70,72], all of these symptoms indicate the presence of COVID-19 infection. These symptoms can be detected through an appropriate medical imaging model of each organ or tissue. Such a broad group of symptoms may occur and continue to the post-COVID syndrome that may last for more than a year [73]. Also, patients may suffer from cardiovascular, enduring pulmonary, endocrine, gastrointestinal, hematologic, psychiatric signs, and neurological [74]. For example, neuroinflammatory mechanisms in addition to the influences of microvascular damages revealed at MR are responsible for severe and continuous neurological symptoms [75,76].

Several studies have demonstrated COVID-19 has significant implications for the Olfactory bulb using the results of CT and MRI that many patients with anosmia have undergone. Where the results of some tests showed that COVID-19 causes an olfactory dysfunction due to the pres-

ence of a change in the shape and size of the olfactory bulb in some people with anosmia caused by COVID-19. There are reports of neurological symptoms in patients with COVID-19, denoted to the neurotropic nature of the virus [52]. Animal surveys displayed that the viral permeation occurs in the olfactory bulb and then spread to the subcortical area and cortical area. In the premier survey from Wuhan, 5.1% and 5.6% of 214 COVID-19 cases had suffered from anosmia and loss of taste, respectively [25].

According to an American study [77], the loss of the sense of smell is strong evidence of infection with COVID-19. A case with a sudden loss of the sense of smell underwent MRI and CT on the nasal sinuses. The result was a normal appearance of the olfactory bulb and olfactory tracts and the presence of bilateral inflammation in the olfactory cleft [78]. Tissues of nasal from patients with post-viral anosmia show severe purulence, missing or fewer cilia on surviving receptor cells [79]. However, the causes of COVID-19 infection are still unknown [80]. A sample of the olfactory epithelium could be used as a source of tissue for primary viral identification to reduce the number of incorrect-negative examination findings [81]. There are two options: (1) a post-viral anosmia syndrome with direct infection and inflammation of the olfactory mucosa and neurodegeneration of the olfactory sensory neurons or (2) an upper respiratory infection with some smell loss as a result of nasal inflammation, mucosal edema, and impediment of the flow of air into the olfactory cleft. Signs of illness development include injury to the peripheral nerve system, as well as its malfunction, such as anosmia or hyposmia [82,83]. A major multicenter European survey reported that 85.6% and 88% of 417 COVID-19 patients experienced olfactory weakness and taste dysfunction, respectively [27]. However, a modern survey from Spain notarized anosmia in 4.9% and loss of taste in 6.2% of 841 patients [84]. In a survey after death, MRI of non-survivors demonstrated the occurrence of olfactory bulb asymmetry and atrophy in 4 of 19 COVID-19 cases [85]. In a case study with screening 4 days after the beginning of anosmia, signal changes of the olfactory bulb in MRI along with a signal increase in the gyrus rectus and bilateral atrophy were documented [69].

The nasal sinuses underwent CT and the olfactory nerves underwent MRI [51]. The measurements were done based on imaging findings to assess the nasal sinuses and opacity of the olfactory clefts. They were:

– **Paranasal Sinus CT**: Based on CT of the sinuses, the ventilation pattern of the olfactory cleft was classified as normal, partial, or whole opacity [51].

– **Olfactory Cleft Opacification**: The olfactory clefts were lined by an olfactory epithelium that contained olfactory receptor neurons. The neurons' axons were carried out as olfactory cilia, which were twisted with the olfactory bulbs through the cribriform plate. The inability of odor to reach the olfactory clefts due to infections of the mucous membranes, in addition to blockage of the nasal cavity. A study relied on CT of the nasal sinuses to assess the opacity of the olfactory clefts showed that the total opacity was 4.3%, while the partial opacity was 69.6%. No cases displayed ethmoid air cells opacification or nasal cavity opacification [51].

– **MRI Assessment**: The method of MRI of nerves was the most appropriate method for anatomical imaging. Therefore, MRI was used to assess olfactory dysfunction associated with post-viral infection, neurodegenerative processes, and trauma. Particularly, the coronal T2 weighted images covering the olfactory bulb anterior pole to the primary olfactory area and conventional sequences for the whole brain [51]. The quantitative measurements were achieved through MRI specific to the olfactory nerves for olfactory bulb volumes, olfactory sulcus depth, qualitative evaluation of olfactory bulb morphology, signal intensity, olfactory nerve cilia measurements, and primary olfactory cortex signal intensity olfactory bulb volumes. The presence of an excessively intense signal in the olfactory bulb appeared in the form of simple bleeding indicating the presence of inflation. Rarity and clustering were used to assess the olfactory nerve cilia. A multi-planar reconstruction (MPR) was used to determine the size of the olfactory bulb [51].

– **Olfactory Sulcus Depth**: The depth to the olfactory sulcus deepest point could be calculated through coronal T2 weighted images. The relationship between the DTI scores and the depth of the right olfactory sulcus was negative. There was no relationship between the DTI scores and the depth of the left olfactory sulcus. There was no relationship between the depth of the sulcus and the sizes of olfactory bulbs [51].

– **Signal Intensity Evaluation**: The appearance of several foci with a very high density in the olfactory bulbs and the presence of high intensity around these foci. The results of MRI which were collected concerning the pattern of the shape and the bulb of the signal proved that there was no statistically meaningful dissimilarity between the sizes of the olfactory bulbs, the scores of DTI, and the depths of the olfactory sulcus. The olfactory nerve cilia structure appeared normally, and clusters appeared [51].

3. Treatment Strategies and Follow-Ups

The current section presents some of the treatment strategies proposed by many researchers that may stop or reduce the infection of COVID-19. Additionally, it presents the importance of follow-up for those recovering from COVID-19, as still many unknown sequelae for those recovered. Therefore, follow-up is necessary for those recovering from COVID-19 to know their clinical needs and discover the unknown long-term sequelae.

3.1 Treatment Strategy of COVID-19

The current subsection presents some of the proposed therapeutic strategies to confront the COVID-19 virus, in-

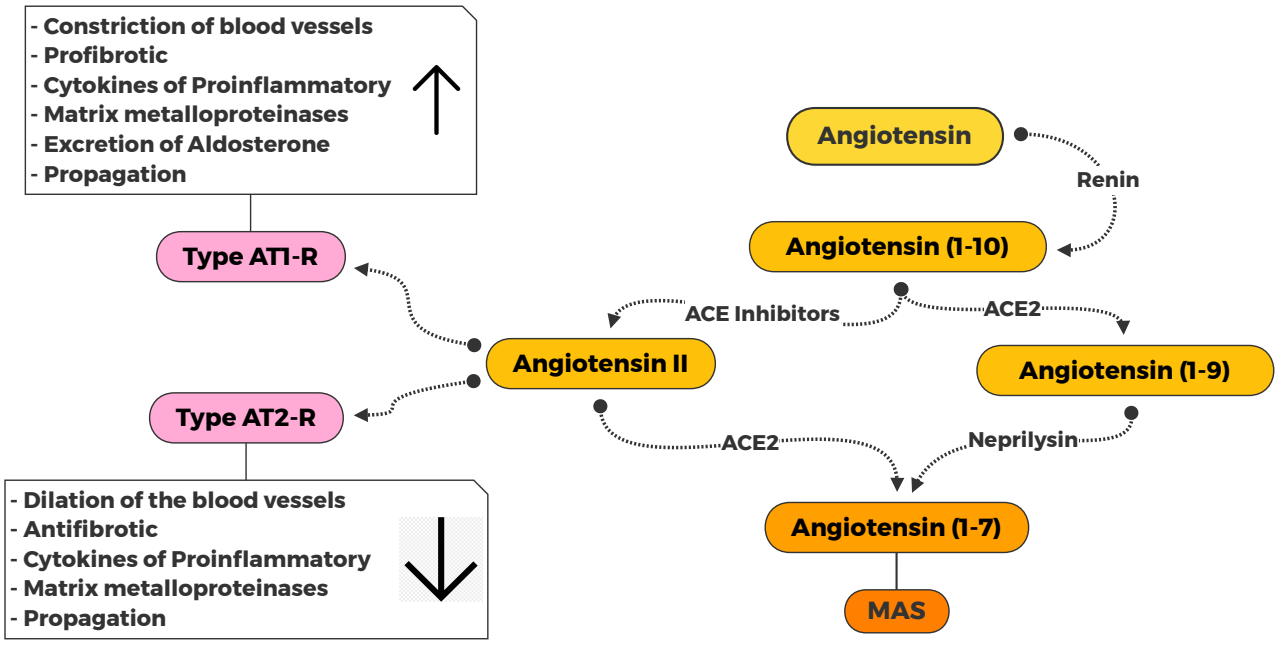

Fig. 5. The treatment strategy summarisation of COVID-19 based on system of renin angiotensin that responsible for adjust high blood pressure.

cluding the role of ACE2 and AT1-R receptors as therapeutic strategies. Modern treatment strategies played an important role in eliminating or decreasing the incidence of COVID-19 infection in the heart, lung, and kidney [86]. Seif *et al*. [86] introduced some strategies for the treatment of COVID-19. The ACE2, angiotensin II receptor type I obstructor (AT1-R obstructors), restraint of ACE, and peptides of angiotensin 1–7 were among the strategies considered. As the ACE2 and AT1-R function critical roles in the improvement of COVID-19, innovative treatment techniques may help to reduce virus-produced heart, lung, and kidney deterioration. Janus kinase inhibitors (JAKinibs) may be useful because they may not only lower medical symptoms in the infected many organs, but they may also control some inflammatory cytokines generated throughout ARDS or tempest of cytokine [86]. There were two potential treatment strategies for COVID-19, namely (1) ACE2 enzyme treatment strategy and (2) receptors of ACE2 for treatment strategy. Fig. 5 summarizes the treatment strategy that will be examined in detail in the subsequent subsections.

3.1.1 ACE2 Enzyme Treatment Strategy

Angiotensin-converting enzyme-2 is the master key for SARS-CoVID and COVID-19. The virus attacks the target cells via the cell protease TMPRSS2. The renin-angiotensin system is a very important regulator of blood pressure, and it is a zinc carboxypeptidase that limits the activity of the potent vasopressor peptide angiotensin II by eliminating the terminal residues of phenylalanine to obtain heptapeptide [87]. ACE2 is plentifully available in the brain, lung, kidney, liver, heart, intestine, and testes [88]. The angiotensin-converting enzyme interacts with the spike protein on the surface of the virus [89]. This interaction leads to activation of the disintegrin, metalloprotease17 (ADAM17) [90]. This reaction results in the elimination of the ACE2 enzyme present in the target cells, thus, generating greater levels of AngII and hyaluronan that contribute to the exacerbation of acute respiratory distress syndrome that leads to death [91].

Therefore, therapeutic strategies based on soluble ACE2 or ACE2 antibodies can reduce the interaction between COVID-19 and ACE2. Also, according to the administration of soluble receptor-binding domain (RBD), the basic domain derived from spike protein on the surface of the virus may prevent the virus from entering cells because it contains 193 amino acids and it can connect with ACE2 [92].

3.1.2 Receptors of Angiotensin II for Treatment Strategy

AT1-R and AT2-R are two types of G-protein-coupled receptors through which AngII can function. AT1- R is responsible for the majority of cardiovascular work, while the adult cardiovascular system contains very little AT2-R. There is a proposed treatment for COVID-19 through angiotensin II receptor blockers (e.g., losartan, valsartan, telmisartan, and candesartan). A study showed that older patients who have other comorbidities with COVID-19 and who were given antihypertensives such as angiotensin receptor blockers are less susceptible to lung injuries [93].

Angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, Ang (1–7) peptides, ACE2, and aldosterone synthase inhibitors are all sug-

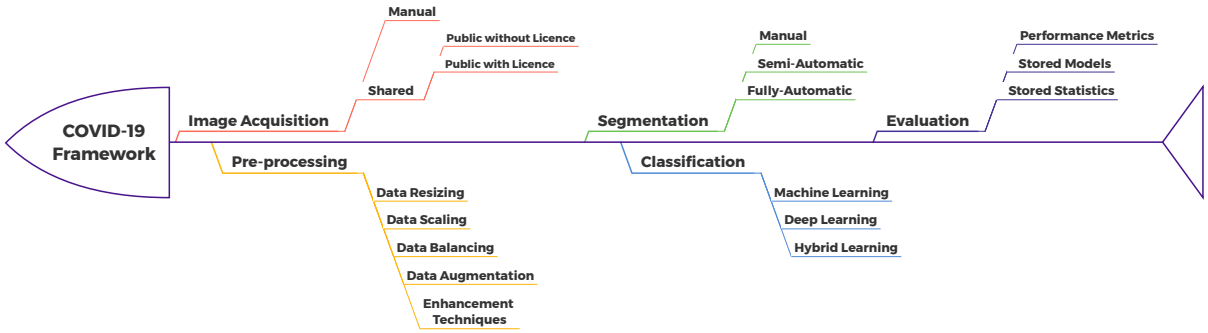

Fig. 6. The base phases on diagnosing COVID-19 using AI.

gested strategies that may prevent or limit heart and lung injuries caused by COVID-19 [94]. Despite this, abrupt discontinuation of these inhibitors may cause problems in some patients at high risk in the case of COVID-19 infection [95]. For some people with ARDS, this syndrome may occur due to the production of excessive levels of inflammatory cytokines, including IL-1, IL-2, IL-6, IL-7, IL-10, and TNF-α. Therefore, Janus Kinase is a novel strategy to control COVID-19, as JAK acts to regulate the immune system [35].

The plasma of people recovering from COVID-19 infection is considered a treatment strategy for COVID-19. The plasma of the recovered people can identify the antibodies to the virus. It is preferable to inject patients at an early stage of infection with plasma from people who have recovered from COVID-19 [96].

3.2 Follow-Up after Recovering from COVID-19

The current subsection presents the importance of conducting follow-ups with recovering persons from COVID-19 to know their clinical needs. Follow-up is carried out in different ways, e.g., assessments of the body by assessment of the respiratory system and other assessments for different organs, through the follow-up stage, the long-term sequelae of COVID-19 can be detected.

Arnold *et al.* [97] presented an investigation into the follow-up phase of COVID-19 patients. The average follow-up period was about 90 days from the onset of COVID-19 symptoms, and their study included 110 people. The participants underwent several tests, including spirometry, exercise test, blood tests, and chest radiography. Their results were as follows: 39% had difficulty breathing, 7% had normal oxygen levels, 39% had severe fatigue and decreased physical ability, 5 patients had abnormalities on chest radiography, 12 patients had liver abnormalities, and 9 patients had abnormal kidney function. A decreased lymphocytes were found in 2 of the participants and an increase in the level of CRP in found 2 of the participants [97].

The consequences of COVID-19 after clinical treatment are still unknown. Therefore, Rovere *et al.* [98] investigated the consequences of COVID-19 in a follow-up phase to determine the clinical requirements of those recovering from COVID-19. The study included 453 followers, who underwent a multidisciplinary assessment by conducting several tests, i.e., pulmonary function (physical examination, blood oxygen level, respiratory rate, and lung function assessment), cardiovascular assessment, and neurological assessment as well. The results proved that those recovering from COVID-19 in the follow-up phase still suffer from some symptoms of COVID-19, such as low oxygen levels, which leads to difficulty breathing, decreased lymphocyte count, and elevated CRP levels [98].

4. Ai-Based Systems for Diagnosing COVID-19

Artificial intelligence (AI) plays an important role in diagnosing diseases such as breast cancer [40], liver cancer [99], renal cancer [100], brain cancer [101], heart failure [102], and recently COVID-19 [103,104]. It is also possible to utilize AI to detect and anticipate massive epidemics. The rapid increase in the number of infections has prompted the use of AI approaches to forecast the likely result of a person infected to provide suitable therapy. Most of the studies share base phases including data retrieval (i.e., acquisition), data pre-processing, segmentation, and classification [105]. The phases can be summarized in a framework as shown in Fig. 6.

4.1 Image Retrieval and Acquisition

The first phase focuses on how the datasets can be retrieved. There are two common paths. The first is getting the data manually from organizations, hospitals, and clinics. The advantage of this approach is that the researcher can manage the styles of the obtained cases. However, the drawbacks are time consumption and potential leakage of protected health information in annotations [106]. The second path is working on anonymized, shared datasets that can be available to the public with or without license agreements. It is worth mentioning that, most of the datasets related to COVID-19 comprise images [107]. Currently, many COVID-19 datasets are available online on different platforms such as Kaggle and GitHub. Table 1 (Ref. [108–110]) summarizes some of these datasets.

Table 1. The discussed COVID-19 datasets summarization.

Dataset	Link	Type	Size	Classes
COVID × CXR-2 [108]	https://www.kaggle.com/andyczhao/COVIDx-cxr2	X-Ray	16.8K	Positive and Negative
COVID × CT [109]	https://www.kaggle.com/hgunraj/COVIDxct	CT	195K	Normal, Pneumonia, and COVID-19
Chest X-ray (COVID-19 and Pneumonia)	https://www.kaggle.com/prashant268/chest-xray-COVID19-pneumonia	X-Ray	6.4K	Normal, Pneumonia, and COVID-19
CT Scans for COVID-19 Classification [110]	https://www.kaggle.com/azaemon/preprocessed-ct-scans-for-COVID19	CT	19.6K	Non-informative, Positive, and Negative

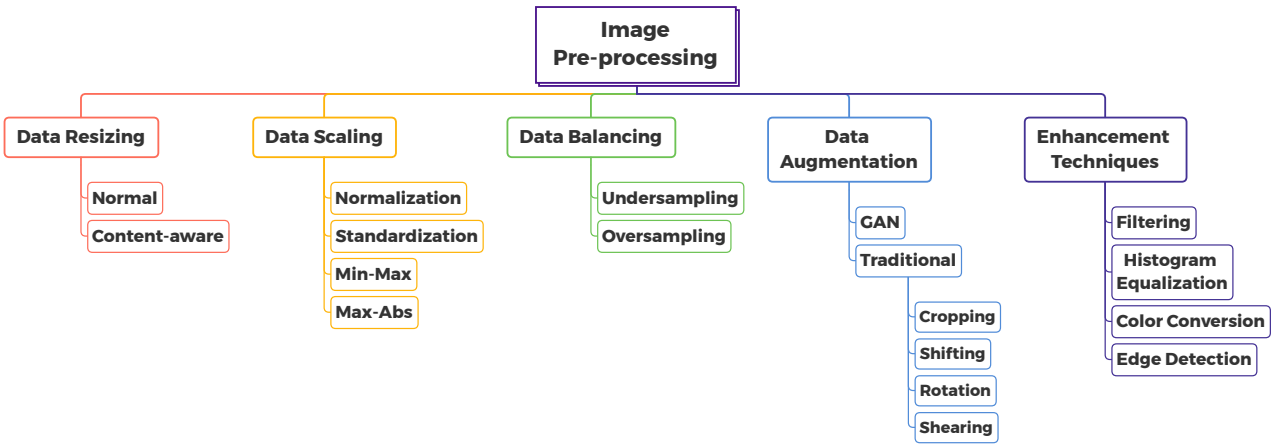

Fig. 7. Summarization of the image pre-processing techniques.

4.2 Image Pre-Processing

The second phase is the pre-processing which focuses on enhancing the quality of images, balancing the sizes, and augmenting them. There are different pre-processing techniques and selecting the sui ones requires deep knowledge and experimental trials [111]. It is proven that the pre-processing techniques enhance the overall performance value [112]. Fig. 7 summarizes the image pre-processing techniques.

4.2.1 Data Resizing

Data or image resizing focuses on changing the dimensions of an image to a target size (i.e., width and height) [113]. There are multiple resizing techniques such as nearest-neighbor interpolation, bilinear and bicubic algorithms, and Fourier-transform methods. In addition to that, there are content-aware resizing methods such as seam carving [114].

4.2.2 Data Scaling

Scaling techniques are responsible for changing the scale of the image data range. There are different scaling techniques such as normalization, standardization, min-max, and max-abs scalers [115]. Kand *et al.* [116] used normalization and standardization while Ahsan *et al.* [117] used the four mentioned techniques.

4.2.3 Data Balancing

Data balancing techniques target to equalize the number of records in each category (i.e., class). There are two common approaches. The first is the undersampling while the second is the oversampling. In the undersampling approach, only some records from the majority class are selected. The number of the selected records is equal to the number of records in the minority class. On the other hand, in the oversampling approach, copies from the minority class are created. The number of the created records is equal to the number of records in the majority class. Reshi *et al.* [118] used one of the data balancing approaches.

4.2.4 Data Augmentation

Data augmentation is useful to increase the diversity of the images. It can be implemented using generative adversarial networks (GAN) or traditional approaches such as shifting and shearing. Khalifa *et al.* [119] used GANs to augment their COVID-19 dataset. Bao *et al.* [120] proposed the COVID-GAN to estimate mobility under various real-world conditions. Traditional approaches include cropping, shifting, shearing, brightness changing, rotation, and zooming. Monshi *et al.* [121] used resizing, rota-

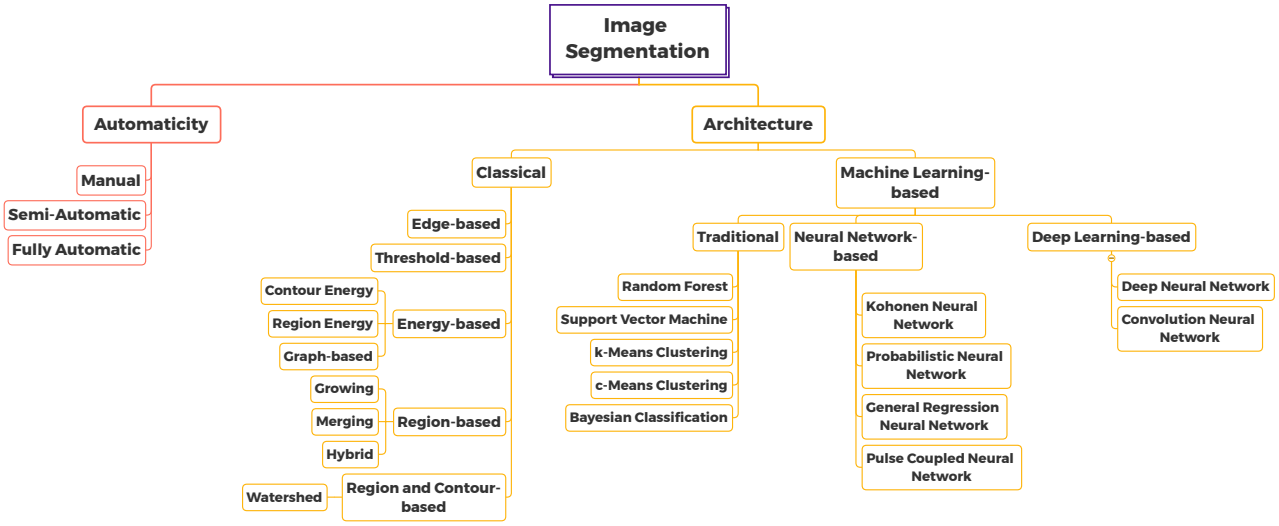

Fig. 8. Image segmentation taxonomy.

tion, zooming, wrapping, lightening, flipping, and erasing in their augmentation pipeline.

4.2.5 Enhancement Techniques

There are different image enhancement techniques such as applying filters, histogram equalization, color conversion (i.e., grayscale conversion and binarization), and edge detection [122]. David *et al*. [123] studied the impact histogram equalization and color mapping in the COVID-19 detection task. Siracusano *et al*. [124] combined the bidimensional empirical mode decomposition with the contrast limited adaptive histogram equalization (CLAHE) algorithm.

4.3 Image Segmentation

Image segmentation can be categorized concerning different points of view. The first point of view is the level of automation that includes three different categories: (1) manual, (2) semi-automatic, and (3) fully automatic. The manual approach requires expert intervention. This approach is time-consuming but effective. The semi-automatic approach injects computer image processing methods and techniques into its working pipeline. Human interaction is required in the initialization, feedback, and evaluation processes. Lastly, the fully automatic approach required no human interaction [125]. The second point of view is the architecture that can be categorized into classical and machine learning- based techniques. The machine-learning-based techniques can also be categorized into traditional, neural network-based, and deep learning-based techniques [126]. Fig. 8 summarizes the image segmentation techniques.

Chakraborty *et al*. [127] proposed a method named SuFMoFPA which is used to segment the radiological images. They used the type-2 fuzzy clustering system and used the super-pixel concept to process the spatial information of the CT scan images efficiently. Yan *et al*. [128] proposed a deep convolutional neural network to segment the CT scan images. They reported dice similarity values of 0.726 and 0.987 for COVID-19 and lung segmentation respectively. Muller *et al*. [129] suggested a segmentation model which was based on the standard 3D U-Net. They reported dice similarity values of 0.761 and 0.956 for COVID-19 and lung segmentation respectively. Abd Elaziz *et al*. [130] proposed a method named MPAMFO. They depended on enhancing the Marine Predators Algorithm (MPA) performance using the moth-flame optimization (MFO) operators. Singh *et al*. [131] proposed the FFQOAK (FFQOA + KMC) which is based on the fast forward quantum optimization algorithm (FFQOA) and K-means clustering (KMC) algorithm. Liu *et al*. [132] suggested the CLACO which is based on the ant colony optimization, the greedy Levy mutation, and the Cauchy mutation. Table 2 (Ref. [127–132]) summarizes the discussed related studies.

4.4 Image Classification

In the image classification phase, the target model focuses on selecting the most suitable parameters aiming to reach state-of-the-art performance in the evaluation process. There are different classification algorithms. They can be categorized into machine learning-based, deep learning-based, and hybrid learning- based algorithms. In the machine learning-based category, the algorithm accepts the features as inputs as it can't extract them automatically. Random forest and decision trees are examples. In the deep learning-based category, the features are extracted automatically and hence the algorithm accepts the raw data as inputs. Lastly, in the hybrid learning-based category, multiple algorithms can be combined sequentially (i.e., multi-stage) or in parallel [133]. Fig. 9 summarizes the classification categories and techniques.

Table 2. Summarization of the COVID-19 related studies concerning image segmentation.

Reference	Approach	Dataset type
Chakraborty *et al.* [127]	SuFMoFPA with type 2 fuzzy clustering system	CT
Yan *et al.* [128]	Deep convolutional neural network	CT
Muller *et al.* [129]	3D U-Net-based model	CT
Abd Elaziz *et al.* [130]	MPAMFO	CT
Singh *et al.* [131]	FFQOAK	CT
Liu *et al.* [132]	(FFQOA + KMC) CLACO	X-Ray

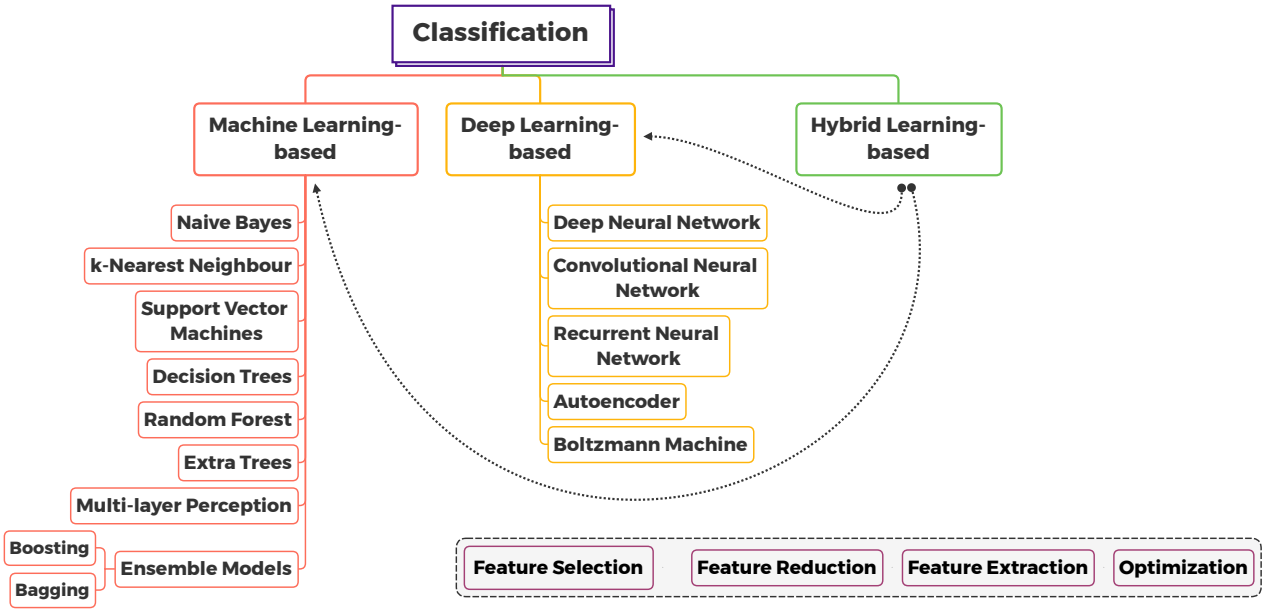

Fig. 9. Classification categories and techniques taxonomy.

As mentioned, machine-learning-based techniques require the features as inputs, and hence feature selection, reduction, and extraction can be used. Feature selection is the process of filtering irrelevant or redundant features [134]. Feature extraction is the process of creating new features that express useful information. Feature reduction is the process of combining two or more features into one or more features where the output features are less than input features [135]. Optimization plays an important role in the classification process. It can accelerate reaching the global (or approximate) optimum targets. It can be used to optimize the parameters (i.e., weights) and hyperparameters (i.e., training configurations). Nadam, Adam, and AdaGrad are examples of the parameter optimizers that can be used with deep learning while genetic algorithms, Sparrow search algorithm [136], and Manta-Ray foraging algorithm [137] are examples of the meta-heuristic optimizers that can be used in both (i.e., parameters and hyperparameters) [138,139].

4.5 System Evaluation

The current subsection introduces the performance metrics that can be used to evaluate artificial intelligence-based systems. Also, they can be used to compare the state-of-the-art approaches concerning the segmentation and classification processes.

4.5.1 Performance Metrics

Sensitivity is the ability to identify diseased patients correctly. Specificity is the ability to identify non-diseased people correctly. Precision is a basic measurement for determining the number of patients accurately recognized in a dataset with an uneven class distribution. The properly identified patients' number in an uneven category dataset among all the patients who may have been foretold is known as recall. The F1 score achieves the ideal equilibrium of recall and precision, allowing for a proper assessment of the model's execution in categorizing patients with SARS-COV-2. The Dice similarity coefficient is a reproducibility validation metric and a spatial overlap index that represents a similarity metric between the ground truth and the prediction score maps [140]. Eqns. 1 to 6 show the mentioned performance metrics where *TP* is the true positive, *FP* is the false positive, *TN* is the true negative, and *FN* is the false negative.

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN} \quad (1)$$

Table 3. Summarization of the COVID-19 related studies concerning classification algorithms.

Reference	Year	Approach	Dataset type	Dataset size	Best performance
Zoabi *et al.* [142]	2021	Gradient boosting and decision trees	Numerical records	51,831	0.90 AUC
Kassania *et al.* [143]	2021	DenseNet121 feature extractor with Bagging tree classifier	X-Ray and CT images	137	99% accuracy
Afshar *et al.* [144]	2021	N/A	CT images and numerical ecords	305	N/A
Khuzani *et al.* [145]	2021	Multi-layer neural network	X-Ray images	420	94% accuracy
Oh *et al.* [146]	2020	Probabilistic Grad- CAM	X-Ray images	502	88.9% accuracy

N/A, Not applicable.

$$\text{Specificity} = \text{TNR} = \frac{TN}{TN + FP} \tag{2}$$

$$\text{Precision} = \text{PPV} = \frac{TP}{TP + FP} \tag{3}$$

$$\text{Recall} = \text{Sensitivity} = \text{TPR} = \frac{TP}{TP + FN} \tag{4}$$

$$\text{F1} = \frac{2 \times \text{Precision} \times \text{Recall}}{\text{Precision} + \text{Recall}} \tag{5}$$

$$\text{Dice} = \frac{2 \times TP}{2 \times TP + FP + FN} \tag{6}$$

4.5.2 State-of-the-Art Systems Comparisons

Kwekha *et al.* [141] reviewed 14 published articles to investigate the machine learning role and how it deals with COVID-19. They concluded that supervised learning is better than unsupervised learning as it had 92.9% testing accuracy. Zoabi *et al.* [142] created a machine learning-based system that was based on gradient boosting with decision trees. They trained it on 51,831 records where 4769 of which were COVID-19 cases. They made their data available in English at https://github.com/nshomron/COVIDpred. They reported 0.90 AUC, 87.30% sensitivity, and 71.98% specificity. Kassania *et al.* [143] used the deep learning-based approach by testing the MobileNet, DenseNet, Xception, ResNet, InceptionV3, InceptionResNetV2, VGGNet, and NASNet transfer learning models. They validated their models only with public X-Ray and CT datasets. They concluded that the DenseNet121 feature extractor with Bagging tree classifier reported the best performance with 99% accuracy. Afshar *et al.* [144] collected the COVID-CT-MD dataset that contained 169 positive, 60 CAP, and 76 normal cases. They compared their dataset with another 8 datasets.

Khuzani *et al.* [145] collected 420 X-Ray images and resized them to (512, 512). Their dataset was grouped into three classes (i.e., COVID-19, pneumonia, and normal). They used a multi-layer neural network with two hidden layers and reported 94% accuracy after 33 epochs. They made their work and dataset available at https://github.com/abzargar/COVID-Classifier.git. Oh *et al.* [146] inspired their approach from the statistical analysis of the potential imaging biomarkers of the X-Ray images. They worked on the segmentation and classification tasks and applied them to public datasets. They proposed a probabilistic Grad-CAM saliency map that is tailored to the local patch-based approach. They reported 88.9% and 79.8% classification accuracies with and without masks respectively. Table 3 (Ref. [142–146]) summarizes the discussed related studies. The table is ordered in a descending order concerning the publication year.

5. Limitations

The limitations of the current survey can be summarized as follows:

– The sample size used by the studies of this survey to conduct various tests and examinations to confirm the results of infection with COVID-19 infection is rather small.

– Cases of COVID-19-associated anosmia were subjected to medical imaging several months after the onset of olfactory impairment, so imaging results indicate moderate changes, not acute or chronic changes.

– Loss of smell and olfactory bulbs still have unclear changes that need more future studies to explain. So far, no unified treatment strategy for COVID-19 infection has been obtained that suits all patients in the world.

– All the proposed strategies are under trial and used according to the biological nature of the patient's body and the response of each patient.

– All of the COVID-19 drugs mentioned in this survey are still under trial until a drug suitable for all patients and designated for COVID-19 infection is obtained.

– In general, there is a need for more studies on every-

thing related to COVID-19 in the future to reach accurate results so that the appropriate treatments for the virus can be known.

6. Conclusions and Future Work

In this survey, we reviewed the COVID-19 infection and its repercussions on many organs such as the lung, heart, brain, kidney, and other organs. We presented the symptoms for the short and long-term. We discussed the impacts of COVID-19 on olfactory bulb and We presented the reasons for olfactory dysfunction and anosmia related to COVID-19 by performing various measurements based on the results of some types of medical imaging in many different studies. We also reviewed the latest therapeutic strategies needed to confront COVID-19 infection, such as the strategy of using ACE2 enzyme and the strategy of using AngII receptors. We discussed some of the follow-up tests that have been done for people who have recovered from COVID-19, through which we can identify the unknown long-term sequelae of the COVID-19 virus. Finally, we discussed some of the artificial intelligence systems and rules that are used to predict and diagnose COVID-19. In the future, we hope to arrive at a radical treatment strategy that is sure and reliable as a direct, safe, and effective treatment for the COVID-19 virus and strengthen the role of artificial intelligence in forecasting, early detection, diagnosis, as well as treatment.

Author Contributions

Conceptualization—ME, HB, MSh, AA, MGho, FS, AM, AE, FT, MSa, MGha, AEB; Project administration—AEB; Supervision—AE, MSa, AEB; Writing – original draft—ME, HB, MSh, AA, MGho, FS, AM, AE, FT, MSa, MGha, AEB; Writing – review & editing—ME, HB, MSh, AA, MGho, FS, AM, AE, FT, MSa, MGha, AEB.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors declare no conflict of interest.

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