

Direct and indirect neurological, cognitive and behavioral effects of COVID-19 on the normal elderly, Mild-Cognitive-Impairment and Alzheimer's Disease populations

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Abstract

This article reviews the main articles that have been published so far about the direct and indirect effects of the COVID-19 pandemic on a particularly fragile population represented by the healthy elderly people as well as those with Mild Cognitive Impairment and Alzheimer's disease. Such populations have been among the most affected in the early stages of the pandemic due to the direct effects of the virus and numerous indirect effects now emerge and will have to be carefully assessed over time. The pandemic associated to COVID-19 has shifted most of the health resources to the emergency area and has consequently left the three main medical areas that dealing with the elderly population (oncology, time-dependent diseases and degenerative disease) temporarily "uncovered". In the phase following the emergency, it will be crucial to guarantee to each area the economic and organizational resources to quickly return to the level of support of the pre-pandemic state. The emergency phase represented an important moment of discussion on the possibilities of telemedicine which will inevitably become increasingly important but all the limits of its use in the elderly population have to be considered. In the post-lockdown recovery phase, alongside the classic medical evaluation, the psychological evaluation must become even more important for doctors caring about people with cognitive decline.

Introduction

The novel coronavirus-2 (SARS-Cov-2) has spread all over the world starting from China in the beginning of 2020 and national health systems had, subsequently, to cope with primary and secondary hits from the SARS-Cov-2 related disease called COVID-19.

COVID-19 results in an outbreak of respiratory disease ranging from mild (a- or pauci-symptomatic) to fatal. Many patients require intensive care with ventilatory support. Critically ill patients suffering from Acute Respiratory Distress Syndrome (ARDS) are by definition hypoxemic, in need of mechanical ventilation and oxygen-therapy, as life-saving strategy. Nevertheless, Ventilator-Induced Lung Injury (VILI) represents a potential adverse effect of mechanical ventilation, which further complicates treatment of these patients[1, 2]. ARDS secondary to interstitial pneumonia is often complicated by multi-organ failure including cardio-vascular and neuromuscular symptoms requiring Intensive Care Unit (ICU) intervention with ventilatory support.

Studies evaluating COVID-19 patients who have heart damage show that it is associated with worse outcomes and that arrhythmic events are not uncommon[3]. Furthermore, elderly subjects with comorbidities -namely hypertension, coronary artery disease or diabetes- are more susceptible to SARS-CoV-2 infection with more severe symptoms and worse outcomes. It is unclear whether cardiac conditions are provoked by COVID-19 or are just comorbidities or non-specific complications of infection. Indeed, a number of COVID-19-related damages to brain structure have been described: from smell/taste impairment to Guillain-Barre-Syndrome, from trigeminal neuralgia to a necrotizing hemorrhagic encephalopathy[4, 5] and behavioral disturbances. In some case, mental confusion, delirium and lethargy appeared before the classic symptoms of fever and respiratory distress. Coagulopathies with a pro-thrombotic condition and an inflammation-related "cytokine tempest" may contribute to the multiorgan damage, including secondary effects on the brain [6–8].

Following the acute stage, a post-acute phase is often encountered characterized by a combination of sequelae combining problems stemming from respiratory, prolonged bedding, cardio-vascular and neurological (including

cognitive/behavioral) complications which inhibit immediate home re-entry of Patients from ICU and COVID-Units.

The great contagiousness of the virus and the high rate of serious and fatal complications has required extraordinary measures including progressive blocking of national borders, banning of non-urgent commercial and health activities, until the adoption of the complete lockdown, at the beginning in China, then in Italy and in Europe and subsequently all over the world. Secondary consequences of the pandemic have involved many chronic diseases, including dementia. Most of the health structures dedicated to follow up of patients with mild cognitive impairment (MCI) and Alzheimer's Disease (AD) and other types of dementia has been down-graded in their activity given the need to implement safety protocols that limited patient access. Outpatient or day hospital activities have been severely reduced or totally closed for a period of about 3 months. Moreover, patients living in 'resting homes' were progressively deprived of the physical visits of their relatives and friends due to safety protocols.

As to June 27 more than 10 million cases were reported causing more than 500.000 deaths. In Italy, which was one of the countries affected earlier by the pandemic after China and where epidemiological data are available for a longer period of time, it has been described that COVID-19 lethality was less than 2.8% for people under 60 years old, rose to 10.6% in the 60-69 age group, 26% in the 70-79 age group, and 32.8% in the 80 year old age group. Within the frame of the more than 35,000 people who died in Italy due to COVID-19, about 20% were between 70 and 79 and about 65% over 60 years of age [9]. The vast majority of them were defined "fragile elderly subjects" namely suffering from 2 or more chronic major diseases on top of which COVID-19 impacted as a final push to death. Although less clear, the data coming from the European Union[10], from the USA[11] and from Brazil[12] describe the same effects on different ages. Taken together, these data clearly define how the risk of severe and fatal complications is higher in the elderly population.

WHO Mental Health Department recently released (January 2020) the document "*Considerations on mental health and psychosocial well-being during the pandemic COVID-19*"[13]. This document is mainly addressed to different groups of the population in support of their mental and psychosocial well-being, among which emerges a specific note to the elderly, caregivers and people with pre-existing diseases: "*during the epidemic and quarantine, the elderly and people with cognitive impairment or dementia, especially if hospitalized in the structure, may experience greater anxiety, anger, stress, agitation or, vice versa, they can close themselves more in themselves*". For people with dementia it can be difficult to fully understand and remind the reasons for this period of isolation and the motivation for whose everyday life has so remarkably changed. The current situation can easily provoke episodes and emotional states that remarkably modify the daily routine and the ordinary coping skills of patients and their families. Sometimes, in fact, a sudden change in behavior of the family members and of daily activities, can trigger or amplify agitation and aggressive reactions in demented patients. Families and senior communities were not prepared to handle an emergency in the emergency and caregivers are likely to need additional and stronger social, financial and psychological support.

In our review we searched on Pubmed, Google Scholar and MedRxiv with the following key terms: "COVID-19", "SARS-CoV2", "Pandemic", "human", "Psychology", "Psychiatry", "Mental Health", "Elderly", "Fragile People", "Mild Cognitive Impairment", "Alzheimer's Disease", "Dementia". Lately, some new reports related to COVID-19 and psychosocial impact on fragile populations as represented by normal elderly and dementia patients, have been critically added.

Direct Consequences Of Covid-19 On Elderly Population And Dementia

At present it is still unclear whether the SARS-CoV-2 virus, an RNA virus, has a direct neurotropic effect. To date, the virus is known to have several close sequence homologies with SARS-CoV-1 and both exploit the enzyme 2 receptor (ACE2) that converts angiotensin to mammalian cells as a binding site. After attachment to the host surface, the virus penetrates through the transmembrane protease serine protease 2 (TMPRSS2) and the viral cycle begins. It therefore appears that the viral cell tropism in humans is mainly determined by the presence of the ACE2 receptor which is expressed in the airways, kidney cells, small intestine, pulmonary parenchyma, testicles and vascular endothelium throughout the body but also has a wide distribution in the central nervous system at the level of neurons, astrocytes and oligodendrocytes[14].

For what it concerns the brain the ACE2 receptor was found in high concentrations in the mouse in substantia nigra, ventricles, middle temporal gyrus, posterior cingulate cortex and olfactory bulb, as well as in the motor cortex and brain stem [15] and this distribution may explain some neurological complications in patients with COVID-19 as a result of possible entry pathways represented by the olfactory bulb and the vascular endothelium.

In a study by Mao et al.[16] it has been shown in 214 patients that the SARS-CoV-2 virus has a potential for penetration of the central nervous system. A percentage of COVID-positive patients had nonspecific neurological symptoms such as dizziness, headache and seizures, or more specific disorders such as loss of smell or taste and stroke. It was then hypothesized how SARS-CoV-2 penetrates through the binding to the enzyme receptor of the human angiotensin converting enzyme 2 (ACE-2) expressed in glial cells and neurons. According to this hypothesis, the way of entry into the brain was suggested to be the nasal olfactory epithelium through the cribriform plate, which can explain the first results of COVID-19 as an altered sense of smell or hyposmia; interestingly enough, this entry path is adjacent to brain areas that are most interested in the development of AD. On a collateral basis, it has also been reported how the SARS-CoV-2 virus can determine, alongside the respiratory infection, a neuroinflammatory state possibly triggering or accelerating neurodegeneration mechanisms and related symptoms including neuropsychiatric ones [17]. This hypothesis, which still needs to be confirmed, could possibly explain long-term indirect neurodegenerative effects in people over 65 years of age. To date, reports of neuro-psychiatric effects related to COVID-19 remain anecdotal and long-term consequences are still far to be documented and need careful monitoring by the scientific community.

The effects of the SARS-COV-2 virus against specific populations of patients at risk can be considered according to 7 key parameters that have been proposed by the National Academies of Sciences, Engineering, and Medicine: *Confirmed Cases, Fraction of Viral Positive, Hospitalizations, Emergency Department Visits, Reported Confirmed COVID-19, Deaths Excess Deaths, Representative Prevalence Surveys*[18]. To date, no specific studies have demonstrated that the MCI or AD conditions increase the risk of a COVID-19 infection and higher fraction of viral positive population, but increased age and associated health conditions such as dementia may increase the risk in this vulnerable population. People affected by AD may forget common measures for lowering the risk of infection as washing their hands, social distance and face masks or taking other necessary precautions. The role of family members and caregivers is crucial by stimulating positive behaviors to reduce risk of contagion. The Center for Disease Control of the U.S.[11] has proposed particularly strict risk reduction measures for people with a history of dementia with specific suggestions such as reminders useful for remembering the main hygiene practices every day, putting alerting signals in the bathroom and elsewhere to remind people with dementia to wash their hands with soap for 20 seconds and having demonstrated the correct accurate hand washing with a

solution based on at least 60% alcohol. For people who are guests of long-term resting homes, alerts have been given to avoid visits from the family members if there are signs or symptoms of illness.

As a result of the infection, older people with dementia develop a more serious disease with more severe symptoms. Although accurate estimates of the mortality rate associated with this disease do not yet exist, it appears that the access rate in emergency facilities, hospitalization and mortality from COVID-19 may be higher in the AD population than in elderly non-demented one. In fact, it should be taken into account that advanced age and concomitant disabling medical conditions such as heart or lung disease or diabetes increase the risk of severe progression and death by COVID-19, which often follows serious effects on the lungs and this condition may still worsen in institutionalized elderly. The immune system of older people already appears constitutionally to be less able to fight infections. In a recent report[19], 80 percent of all deaths from COVID-19 in the United States were among adults 65 years of age and older and the rate of serious outcomes was higher between 85 and years of age.

Interestingly, it was also hypothesized[20] that two commonly used drugs for Parkinson (amantadine) and AD (memantine) might play a protective role against SARS-CoV-2 infection through an inhibition of neurotoxicity and viral replication with slowing of the pathological phenomenon that leads to the development of ARDS. This is because of the role of Memantine, which acts as a non-competitive N-methyl-D-aspartic acid receptor (NMDA) antagonist by preventing excess calcium in cells. This property, useful in the treatment of Alzheimer's patients, is similar to that of amantadine, which is used in tremor associated with Parkinson's disease and could have antiviral potential. Although suggestive, this hypothesis still needs to be confirmed.

Ethical considerations regarding COVID-19 and fragile patients with dementia

The COVID emergency has brought into the vocabulary of health operators and decision-makers two words that previously were poorly used: "limited resources". Since the beginning of the crisis it was clear that the huge impact of COVID-19 on emergency departments would lead to the application of severe measures previously adopted during war or natural disasters. The impact of the disease on emergency wards was especially important during the first phase of the pandemic in which the request for beds and life-supporting interventions (i.e. mechanical ventilation with full-head masks) in advanced emergency wards and ordinary therapy, had been far greater than their availability and therefore they were adopted measures to regulate the allocation of the available resources. An analysis of the journal *Financial Times* after the first 3 months of the pandemic has established that the region of northern Italy in Lombardy and in particular the region of Bergamo had recorded an increase in mortality for the same period in previous years of over 660%, for a really sad record that placed it in first place in the world and third in history after the city of Miyagi in Japan during the 2011 tsunami (685%) and the city of Philadelphia during the Spanish Flu of 1918 [21].

The impact of a large number of patients on emergency care departments has prompted many scientific societies to take measures to "optimize" the resources available in terms of medical equipment and personnel. The first guidelines were released by the Israeli resuscitation society indicating that all people affected by severe forms of COVID-19 must be guaranteed adequate palliative care even if clinically compromised and with dementia and as far as possible [22]. A document from some of the Italian anesthesia and resuscitation societies proposed measures to be taken during the triage in emergency department that took into account factors such as age, comorbidities, and the functional status of any critically ill patient potentially admitted in

order to maximize the benefits for the largest number of people [23]. This means -not in theory, but in practice- that in case of shortness of resources, Patients with advanced age and progressive cognitive decline were not candidates for life-support interventions!

Indirect Consequences On Elderly Population And Dementia

It is estimated that over 50 million live with dementia worldwide [24]. In Italy, the total number of patients with dementia is estimated at over one million (of which approximately 600,000 with Alzheimer's dementia) and approximately 3 million people are directly or indirectly involved in caring for their loved ones. During the emergency related to COVID-19, this population was particularly at risk because it was made up of people of advanced age, with limited access to the technological information available through the media and the Web. Such frailty population often lives alone or in medium- and long-term senior houses which were among the places at greatest risk for rapid viral diffusion and unfavorable outcome [25]. Elderly subjects, in particular those with chronic neuropsychiatric diseases, and workers in the health sector seem to be the most exposed individuals to the negative effects of quarantine during an infectious epidemic [26].

A crucial factor to consider in older people in general, and in particular in people with MCI or AD, is to understand what might be responsible for effects greater than the direct effects of the virus for the severity enhancement of pre-existing medical clinical conditions in COVID survivors. For these reasons, it seems appropriate that people who have been affected by SARS-COV-2 continue for a long period of time medical follow-ups aiming to early detection of any alteration in the clinical course of the pathologies from which they were affected before the viral infection[27].

During the pandemic, a crispy scientific discussion was represented by the opportunity or not to isolate those people at risk in long-term residential structures with minimal contact with the outside world in order to limit the diffusion of the infection. A survey carried out in Italy in residential structures that host AD patients[28] revealed that in March 2020 the mortality compared to the same month in previous years was +94%, with peaks of almost +300% in Lombardy, one of the regions most affected. This finding, which has not always been associated with a similar number of patients with nasopharyngeal swab positivity for SARS-COV-2, raises questions about the possible underestimations of the unfavorable effects of the virus on mortality. In many small towns in southern Italy where the outbreaks were scarce or non-existent, the presence of a senior house for AD patients was the main factor identified in turning the whole area into a red area.

For some time now, it has been known that people with dementia and their caregivers present an increased risk of developing psychological complications characterized mainly by deflection of mood and the development of depression and anxiety [29–32]. This condition was further aggravated during the pandemic due to the combined effects of social isolation, limited access to hospital and outpatient healthcare facilities often converted in COVID-Units to cope with the emergency, or because of the fear of developing new infections. Already from the early stages of the emergency in China, it became clear how the role of family associations could be particularly important in disseminating information related to the prevention of COVID-19 infections, subsequently in setting up tools capable of providing psychological support[33, 34].

Patients with severe cognitive impairment due to AD and related dementias therefore represent one of the populations at greatest risk of negative outcomes during quarantine. The decline in cognitive functions and the

inevitable impact of pathology on quality of life it also has serious effects on the family and on the informal caregiver (someone -family member, relative or friend- who assists the sick person at home). The wish of stay close to relatives, to allow the patient to continue living in his own residence and the perception of feeling obliged to take care of them are the main factors behind the choice to assist at home. The caregiver condition, however, is associated with a significant deterioration in quality of life and with an increased risk of disease and death [35].

An integrated assessment of the health of elderly people with initial and advanced forms of dementia should take into account the drugs that are taken daily and their possible effect on the course of COVID-19 infection. All chronic diseases must be considered and it should not be forgotten that all these conditions continue to progress even during the pandemic phase and in the following period. It must be considered that also health aspects that are taken for granted in younger people may not be so for elderly people such as for example a correct management of nutrition with a correct intake of water and food, a correct amount of daily physical and cognitive exercise, a correct management of daily pharmacological therapies and medical devices; all these items and the psychological well-being of frail elderly people who may not have fully understood all the effects of this pandemic must be particularly taken into account[36]. Elderly frail subjects should therefore never be left alone and it is necessary to implement remote monitoring systems for all these chronic medical conditions with particular attention to people who have been infected with the virus.

Impact Of Covid-19 On Research

As SARS-CoV-2 causes severe respiratory symptoms in people aged 60 and over, the implications for patients with AD are important and specific measures have been taken to reduce the impact of contagion in this population. Protective measures for laboratory research operators also blocked studies on transgenic animals with important economic consequences. It should not be forgotten that public health systems and private companies involved in research must and will have to face the economic consequences of this period in the immediate future and it is plausible to think of a period in which investments will be reduced. Data loss in research studies is at the forefront of indirect problems associated with the COVID-19 epidemic[37].

A paradigmatic picture of the COVID-related emergency situation and its impact on research protocols can be obtained by analyzing what happened with the INTERCEPTOR project in Italy, a multicenter study that aims to determine at an early stage the biomarkers associated with early conversion from MCI ad AD and involves 25 centers (20 recruiting centers and 5 expert centers) located throughout the whole national territory[38]. The first problems with recruitment began in February 2020 with a complete cessation of activities starting from 9 March, the date on which the complete *Lockdown* was declared in Italy, and subsequent initial and slow resumption of activities in June. Meanwhile, many candidates and caregivers do not want to come to hospitals for the recruitment/follow-up visits as well as for the acquisition of the biomarkers under study. A report of the difficulties encountered and the solutions adopted is currently being developed for future considerations in the data analysis phase.

Many expected phase 2/3 clinical trials such as that relating to Gantenerumab (Roche) and Solanezumab (Lilly) should give expected results in this period[39] but it is possible that there are variable shifts depending on future developments in the global social framework.

In this area there have been many rumors in favor of a prudent and controlled reopening of the centers dedicated to conducting clinical and preclinical research dedicated to Alzheimer's disease. Although safety of operators and patients must be taken into account, the enormous social and economic impact of a prolonged closure over time must also be considered.

In the reopening mechanisms, an important role is played by telemedicine methods through telephone interviews and video consultations aimed at checking the expected results during the follow-up. Certainly, a complicated aspect is represented by the screening visits which have suffered heavy losses due to the lockdown and will require a precise reformulation in all the clinical studies currently underway and about to start[40, 41].

Telemedicine in Alzheimer's disease and dementia has already demonstrated an excellent development potential, especially as regards to the follow up phase, while indications are still limited in the setting up of the therapeutic path. Several limitations should be considered including the lack of efficient internet connection throughout the territory, a lack of familiarity with the Information and Communication Technology (ICT) facilities by older people and their relatives, the presence of sensory deficits in elderly people such as visual disturbances or hearing disorders that can make technological contact difficult. In addition, it must be considered that in this population of fragile patients, human contact remains a fundamental tool for continuing the therapeutic and rehabilitative path[42, 43].

Both EMA and FDA[44, 45] released official documents asking to different stakeholders involved in clinical trials to respect national legislation and to put people's safety before any situation of possible conflict. For ongoing trials, there it should be considered a longer duration to be agreed with national Authorities for drug approval, for sponsors and investigators and to continue to always report possible adverse events. The details of the closure and reopening must be adequately detailed and taken into account in the discussion of the results.

The totally new situation that we are living has also been acknowledged by the main scientific journals that deal with this area and guidelines have been proposed on the conduct of clinical studies during this phase. For example, it was proposed that clinical trials should be suspended to ensure the safety of participants and both sponsors and investigators should take charge of communication as adequate as possible with the enrolled subjects. In view of the complexity of the research networks that are involved in these researches, public/private funding companies must collaborate toward reopening plans and safeguard the correctness of scientific information. In processing the data, it was necessary to take into account the impossibility of keeping the dates of the follow-up visits within the time windows and these difficulties had to be considered and discussed in the monitors' meetings. It is up to the Review Boards for the various clinical trials to decide and apply measures that safeguard data security and integrity as much as possible. Since many of the studies dedicated to Alzheimer's disease are very long in time and very expensive, the problem of missing data must also be assessed within the general context of the World' trial. The major scientific associations involved in ensuring research on Alzheimer's disease encourage the publication of methodologies with which the various research groups are statistically addressing these problems[46].

Impact Of Covid-19 On Psychiatric Health Of Patients With Cognitive Decline And Their Caregiver

In a recent review on this topic, Brooks et al.[47] have underlined how the negative quarantine effects represented by anger and post-traumatic disorder are associated with negative determinants which can be summarized in the following: quarantine duration, infection fears, frustration, boredom, inadequate supplies, inadequate information, financial loss, and stigma with possible long-lasting effects.

It has also been reported by Ward C.F. and colleagues [48] that an altered mental status of acute onset may be an heralding symptom of COVID. In their report, the Authors described 4 different cases of people who had already received a diagnosis of dementia in which confusion, agitation and disorientation appeared before other respiratory symptoms or fever. In all cases, the search for the viral genome using a nasopharyngeal swab tested positive and all the patients analyzed would have developed radiologically evident pneumonia in a period of 3-7 days and respiratory complications which, in 2 out of 4 patients were of high severity.

The public health measures put in place so far to face the pandemic, have required social isolation which have proven to be the only truly effective prevention strategy [49]. As the advance of the virus continues all over the world involving also America, India and developing countries, the social impact of these measures is still far from being fully understood [50–54] but there is a serious risk that for some population groups this condition will worsen the state of solitude with the appearance of depression. Specific questionnaires have been proposed aimed at investigating how the social isolation necessary to stop the pandemic has influenced communication with other people who play an important role in the daily lives of elderly and demented subjects, starting from the doctor to relatives.

A survey conducted in the Chinese population[55] showed an increase in long-term care insurance (LTCI) purchase intentions from elderly people from 25% to 38% after the COVID-2019 epidemic as an indirect demonstration of an increased perception that the end of life is approaching. These data were particularly marked for people with initial forms of cognitive impairment, who had received the diagnosis in recent times and -because of such diagnosis- had already modified their lifestyle and for whom the COVID-19 effect represented a further rapid phase of decline. In this view, it seems that the emergency had led to growing concern about death in the elderly population and has exacerbated the burden of chronic diseases such as early cognitive decline and dementia.

The first studies on the psychological impact of the pandemic were carried out in China, in the Gansu region, during the first phase of the emergency; health workers were examined in order to understand the prevalence and risk factors of anxiety and depression and any coping strategies for negative emotions[56]. With the use of specific questionnaires, a prevalence of anxiety of 11% and depression of 46% in doctors and 28% and 43.0% in nurses emerged. Such symptoms were more frequent in women and in those who had already experienced psychological symptoms before the pandemic. It also emerged that the adoption of positive coping styles tended markedly to improve negative emotions.

In a Spanish study[57], 40 subjects diagnosed with MCI (20) or mild AD (20) who had performed neuropsychological and clinical assessment during the month prior to the lockdown, were reevaluated after 5 weeks of social isolation via the neuropsychiatric scale (NPI) and EuroQol- 5D. The total basal NPI score worsened by about 6 points, from 33.75 to 39.05 after confinement, with the appearance of various neuropsychiatric symptoms including apathy and anxiety in subjects with MCI and apathy, agitation and

aberrant motor behavior in AD patients. Globally, both patients and their caregivers worsened in about 40% of cases.

Changes in the daily life habits of older people with an interruption of social activities such as the maintenance of public areas as well as volunteering within the community, sports or other leisure activities, could also have a much more important impact on older people because they have developed their own daily routine to fill-up empty spaces left by the lack of working and family duties. The psychological impact of the lockdown could be even tougher for people who have been hospitalized during this period, because of the separation from their loved ones, leading to despair and feelings that the world is ending. A possible solution for all these different situations can be represented by the adoption of coping strategies through techniques that use cognitive and behavioral supports and with the help of qualified personnel to manage anxiety and stress caused by the pandemic [58].

The specific coping strategies suitable for the individual must be planned and executed with the help of qualified personnel. Such adaptive psychological mechanisms with the scope of managing, reducing or tolerating stress associated to COVID-19 have been already proposed for large-scale use for elderly people who have been involved in the pandemic and who have suffered its negative effects without having, sometimes, understood all the seriousness of the COVID-era[59].

Conclusions

The pandemic associated to COVID-19 has shifted most of the health resources to the emergency area and has consequently left the three main medical areas that affect the elderly population (oncology, time-dependent diseases and degenerative disease) temporarily “uncovered”. In the phase following the emergency, it will be crucial to guarantee to each area the economic and organizational resources to quickly return to pre-pandemic state. It must be considered that even people who have not been directly affected by the viral infection may suffer from indirect effects related to the worsening of the background medical condition, to delay of control visits due to organizational difficulties (related to structures and staff) and for the fear of coming in contact with hospitals that have been seen as a major source of infection. The emergency phase represented an important moment of discussion on the possibilities of telemedicine which will inevitably become increasingly important even if the problems related to an optimal use by elderly patients will have to be resolved and all the limits of an evaluation in which there is not direct contact with the patient must be considered. In the post-lockdown recovery phase, alongside the classic medical evaluation, the psychological evaluation -with which doctors need to become more familiar- and the use of specific professional figures will have to find ample space, in order to better understand all the consequences on elderly population that are still not completely evident.

Declarations

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References

1. Li L, Huang Q, Wang DC, et al (2020) Acute lung injury in patients with COVID-19 infection. *Clin Transl Med* 10:20–27. <https://doi.org/10.1002/ctm2.16>
2. Gattinoni L, Carlesso E, Cadringer P, et al (2003) Physical and biological triggers of ventilator-induced lung injury and its prevention. *European Respiratory Journal* 22:15s–25s. <https://doi.org/10.1183/09031936.03.00021303>
3. Wang D, Hu B, Hu C, et al (2020) Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA* 323:1061–1069. <https://doi.org/10.1001/jama.2020.1585>
4. Nath A (2020) Neurologic complications of coronavirus infections. *Neurology* 94:809–810. <https://doi.org/10.1212/WNL.00000000000009455>
5. Baig AM (2020) Neurological manifestations in COVID-19 caused by SARS-CoV-2. *CNS Neurosci Ther* 26:499–501. <https://doi.org/10.1111/cns.13372>
6. Tang N, Li D, Wang X, Sun Z (2020) Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 18:844–847. <https://doi.org/10.1111/jth.14768>
7. Han H, Yang L, Liu R, et al (2020) Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med* 58:1116–1120. <https://doi.org/10.1515/cclm-2020-0188>
8. Wu L, O’Kane AM, Peng H, et al (2020) SARS-CoV-2 and Cardiovascular Complications: from Molecular Mechanisms to Pharmaceutical Management. *Biochem Pharmacol*. <https://doi.org/10.1016/j.bcp.2020.114114>
9. EpiCentro Coronavirus | Istituto Superiore di Sanità. <https://www.epicentro.iss.it/en/coronavirus/>. Accessed 22 Jun 2020
10. ALVAREZ M (2020) COVID-19 Cases and Case Fatality Rate by age. In: Knowledge for policy - European Commission. https://ec.europa.eu/knowledge4policy/publication/covid-19-cases-case-fatality-rate-age_en. Accessed 22 Jun 2020
11. CDC (2020) Coronavirus Disease 2019 (COVID-19) – Prevention & Treatment. In: Centers for Disease Control and Prevention. <https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html>. Accessed 22 Jun 2020
12. Coronavírus Brasil. <https://covid.saude.gov.br/>. Accessed 22 Jun 2020
13. Coronavirus. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>. Accessed 22 Jun 2020

14. Zubair AS, McAlpine LS, Gardin T, et al (2020) Neuropathogenesis and Neurologic Manifestations of the Coronaviruses in the Age of Coronavirus Disease 2019: A Review. *JAMA Neurol.* <https://doi.org/10.1001/jamaneurol.2020.2065>
15. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in human and mouse brain | bioRxiv. <https://www.biorxiv.org/content/10.1101/2020.04.07.030650v1>. Accessed 22 Jun 2020
16. Mao L, Jin H, Wang M, et al (2020) Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol.* <https://doi.org/10.1001/jamaneurol.2020.1127>
17. Hascup ER, Hascup KN (2020) Does SARS-CoV-2 infection cause chronic neurological complications? *GeroScience* 1–5. <https://doi.org/10.1007/s11357-020-00207-y>
18. National Academies of Sciences E (2020) Evaluating Data Types: A Guide for Decision Makers using Data to Understand the Extent and Spread of COVID-19
19. CDCMMWR (2020) Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) – United States, February 12–March 16, 2020. *MMWR Morb Mortal Wkly Rep* 69:.. <https://doi.org/10.15585/mmwr.mm6912e2>
20. Brenner SR The potential of memantine and related adamantanes such as amantadine, to reduce the neurotoxic effects of COVID-19, including ARDS and to reduce viral replication through lysosomal effects. *Journal of Medical Virology* n/a: <https://doi.org/10.1002/jmv.26030>
21. McCann A, Wu J, Katz J (2020) How the Coronavirus Compares With 100 Years of Deadly Events. *The New York Times*
22. Clarfield AM, Dwolatzky T, Brill S, et al (2020) Israel Ad Hoc COVID-19 Committee: Guidelines for Care of Older Persons During a Pandemic. *J Am Geriatr Soc.* <https://doi.org/10.1111/jgs.16554>
23. Vergano M, Bertolini G, Giannini A, et al (2020) Clinical ethics recommendations for the allocation of intensive care treatments in exceptional, resource-limited circumstances: the Italian perspective during the COVID-19 epidemic. *Crit Care* 24:.. <https://doi.org/10.1186/s13054-020-02891-w>
24. O'Connor D World Alzheimer Report 2019: Attitudes to dementia. 160
25. Wang H, Li T, Barbarino P, et al (2020) Dementia care during COVID-19. *Lancet* 395:1190–1191. [https://doi.org/10.1016/S0140-6736\(20\)30755-8](https://doi.org/10.1016/S0140-6736(20)30755-8)
26. Yang Y, Li W, Zhang Q, et al (2020) Mental health services for older adults in China during the COVID-19 outbreak. *Lancet Psychiatry* 7:e19. [https://doi.org/10.1016/S2215-0366\(20\)30079-1](https://doi.org/10.1016/S2215-0366(20)30079-1)
27. Palmer K, Monaco A, Kivipelto M, et al (2020) The potential long-term impact of the COVID-19 outbreak on patients with non-communicable diseases in Europe: consequences for healthy ageing. *Aging Clin Exp Res.* <https://doi.org/10.1007/s40520-020-01601-4>
28. Palmieri L, Vanacore N, Donfrancesco C, et al (2020) Clinical Characteristics of Hospitalized Individuals Dying with COVID-19 by Age Group in Italy. *J Gerontol A Biol Sci Med Sci.* <https://doi.org/10.1093/gerona/glaa146>
29. Gao J, Zheng P, Jia Y, et al (2020) Mental health problems and social media exposure during COVID-19 outbreak. *PLOS ONE* 15:e0231924. <https://doi.org/10.1371/journal.pone.0231924>
30. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA (1988) Cornell scale for depression in dementia. *Biological Psychiatry* 23:271–284. [https://doi.org/10.1016/0006-3223\(88\)90038-8](https://doi.org/10.1016/0006-3223(88)90038-8)

31. Cerejeira J, Lagarto L, Mukaetova-Ladinska EB (2012) Behavioral and Psychological Symptoms of Dementia. *Front Neurol* 3:. <https://doi.org/10.3389/fneur.2012.00073>
32. Schulz R, O'Brien AT, Bookwala J, Fleissner K (1995) Psychiatric and Physical Morbidity Effects of Dementia Caregiving: Prevalence, Correlates, and Causes. *Gerontologist* 35:771–791. <https://doi.org/10.1093/geront/35.6.771>
33. Boots LMM, de Vugt ME, van Knippenberg RJM, et al (2014) A systematic review of Internet-based supportive interventions for caregivers of patients with dementia. *Int J Geriatr Psychiatry* 29:331–344. <https://doi.org/10.1002/gps.4016>
34. Tian F, Li H, Tian S, et al (2020) Psychological symptoms of ordinary Chinese citizens based on SCL-90 during the level I emergency response to COVID-19. *Psychiatry Res* 288:112992. <https://doi.org/10.1016/j.psychres.2020.112992>
35. Chiao C-Y, Wu H-S, Hsiao C-Y (2015) Caregiver burden for informal caregivers of patients with dementia: A systematic review. *Int Nurs Rev* 62:340–350. <https://doi.org/10.1111/inr.12194>
36. Abbatecola AM, Antonelli-Incalzi R (2020) Editorial: COVID-19 Spiraling of Frailty in Older Italian Patients. *J Nutr Health Aging* 24:453–455. <https://doi.org/10.1007/s12603-020-1357-9>
37. Bostanciklioglu M (2020) Severe acute respiratory syndrome coronavirus 2 is penetrating to dementia research. *Curr Neurovasc Res*. <https://doi.org/10.2174/1567202617666200522220509>
38. Rossini PM, Cappa SF, Lattanzio F, et al (2019) The Italian INTERCEPTOR Project: From the Early Identification of Patients Eligible for Prescription of Antidementia Drugs to a Nationwide Organizational Model for Early Alzheimer's Disease Diagnosis. *J Alzheimers Dis* 72:373–388. <https://doi.org/10.3233/JAD-190670>
39. Topline Result for First DIAN-TU Clinical Trial: Negative on Primary | ALZFORUM. <https://www.alzforum.org/news/research-news/topline-result-first-dian-tu-clinical-trial-negative-primary>. Accessed 22 Jun 2020
40. Geerts H, van der Graaf PH (2020) Salvaging CNS Clinical Trials halted due to COVID-19. *CPT Pharmacometrics Syst Pharmacol*. <https://doi.org/10.1002/psp4.12535>
41. Ousset PJ, Vellas B (2020) Viewpoint: Impact of the Covid-19 Outbreak on the Clinical and Research Activities of Memory Clinics: An Alzheimer's Disease Center Facing the Covid-19 Crisis. *J Prev Alzheimers Dis* 7:197–198. <https://doi.org/10.14283/jpad.2020.17>
42. Costanzo M, Signorelli M, Aguglia E (2014) EPA-0715 – Telemedicine and alzheimer: a systematic review. *European Psychiatry* 29:1. [https://doi.org/10.1016/S0924-9338\(14\)78073-3](https://doi.org/10.1016/S0924-9338(14)78073-3)
43. Cuffaro L, Di Lorenzo F, Bonavita S, et al (2020) Dementia care and COVID-19 pandemic: a necessary digital revolution. *Neurol Sci*. <https://doi.org/10.1007/s10072-020-04512-4>
44. FRANCISCO EM (2020) Guidance to sponsors on how manage clinical trials during the COVID-19 pandemic. In: European Medicines Agency. <https://www.ema.europa.eu/en/news/guidance-sponsors-how-manage-clinical-trials-during-covid-19-pandemic>. Accessed 22 Jun 2020
45. Research C for DE and (2020) COVID-19: Developing Drugs and Biological Products for Treatment or Prevention. In: U.S. Food and Drug Administration. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention>. Accessed 22 Jun 2020

46. (2020) Alzheimer's Disease Research Enterprise in the Era of COVID-19/SARS-CoV-2. *Alzheimers Dement* 16:587–588. <https://doi.org/10.1002/alz.12093>
47. Brooks SK, Webster RK, Smith LE, et al (2020) The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet* 395:912–920. [https://doi.org/10.1016/S0140-6736\(20\)30460-8](https://doi.org/10.1016/S0140-6736(20)30460-8)
48. Ward CF, Figiel GS, McDonald WM (2020) Altered Mental Status as a Novel Initial Clinical Presentation for COVID-19 Infection in the Elderly. *Am J Geriatr Psychiatry* 28:808–811. <https://doi.org/10.1016/j.jagp.2020.05.013>
49. Cawthon P, Orwoll E, Ensrud K, et al (2020) Assessing the impact of the covid-19 pandemic and accompanying mitigation efforts on older adults. *J Gerontol A Biol Sci Med Sci*. <https://doi.org/10.1093/gerona/glaa099>
50. Nicola M, Alsaifi Z, Sohrabi C, et al (2020) The socio-economic implications of the coronavirus pandemic (COVID-19): A review. *Int J Surg* 78:185–193. <https://doi.org/10.1016/j.ijisu.2020.04.018>
51. Dubey S, Biswas P, Ghosh R, et al (2020) Psychosocial impact of COVID-19. *Diabetes Metab Syndr*. <https://doi.org/10.1016/j.dsx.2020.05.035>
52. Rajkumar RP (2020) COVID-19 and mental health: A review of the existing literature. *Asian J Psychiatr* 52:102066. <https://doi.org/10.1016/j.ajp.2020.102066>
53. Buonsenso D, Cinicola B, Raffaelli F, et al (2020) Social consequences of COVID-19 in a low resource setting in Sierra Leone, West Africa. *Int J Infect Dis* 97:23–26. <https://doi.org/10.1016/j.ijid.2020.05.104>
54. Chetterje P (2020) Gaps in India's preparedness for COVID-19 control. *Lancet Infect Dis* 20:544. [https://doi.org/10.1016/S1473-3099\(20\)30300-5](https://doi.org/10.1016/S1473-3099(20)30300-5)
55. Xu X, Zhang L, Chen L, Wei F (2020) Does COVID-2019 have an Impact on the Purchase Intention of Commercial Long-Term Care Insurance among the Elderly in China? *Healthcare (Basel)* 8:. <https://doi.org/10.3390/healthcare8020126>
56. Zhu J, Sun L, Zhang L, et al (2020) Prevalence and Influencing Factors of Anxiety and Depression Symptoms in the First-Line Medical Staff Fighting Against COVID-19 in Gansu. *Front Psychiatry* 11:. <https://doi.org/10.3389/fpsy.2020.00386>
57. Lara BB, Carnes A, Dakterzada F, et al Neuropsychiatric symptoms and quality of life in Spanish Alzheimer's disease patients during COVID-19 lockdown. *European Journal of Neurology* n/a: <https://doi.org/10.1111/ene.14339>
58. Thoits P (1995) Stress, Coping, and Social Support Processes - Where Are We - What Next. *J Health Soc Behav* 35:53–79. <https://doi.org/10.2307/2626957>
59. Bavel JJV, Baicker K, Boggio PS, et al (2020) Using social and behavioural science to support COVID-19 pandemic response. *Nature Human Behaviour* 4:460–471. <https://doi.org/10.1038/s41562-020-0884-z>

Table

Table 1. summary table of the papers considered in the review.

Author	Type	Main Findings	Ref.
Li L	Case Series	Lung edema is a manifestation of acute lung injury (ALI) and may progress to hypoxemia and potentially acute respiratory distress syndrome (ARDS). Patients diagnosed with ARDS have poorer prognosis and potentially higher mortality. Neurological complications are associated with poor outcome.	[1]
Wang D	Case Series	Single-center case series of 138 hospitalized patients with confirmed NCIP in Wuhan, China. 36 were transferred to the intensive care unit and 6 died. Neurological impairment is associated with worst outcome	[3]
Nath A	Expert opinion	Considering various brain complications associated with COVID-19 there's need to retool and rethink how train physicians in and physician scientists and how to prioritize drug development for neurologic diseases	[4]
Baig AM	Expert opinion	The SARS-CoV-2 causing COVID-19 can take two pathways to involve the brain. Neurological complications of CNS invasion is rare but not impossible and have to be promptly assessed and treated	[5]
Tang N	Case series	In 183 consecutive patients in China, abnormal coagulation results, especially markedly elevated D-dimer and fibrin degradation product were more common in older people with pneumonia. These mechanisms could explain other complications including neurological features	[6]
Han H	Case series	In 94 patients in Wuhan, China, D-dimer and fibrin degradation product values in patients with severe SARS-CoV-2 infection were higher than those in patients with milder forms, thus explaining vascular complications including stroke	[7]
Wu L	Review	Several mechanisms have been postulated for COVID-19-associated organ damage including SARS-CoV-2 receptor angiotensin-converting enzyme 2 (ACE2) activation, cytokine storm, hypoxemia, stress and cardiotoxicity of antiviral drugs.	[8]
Alvarez M	Epidemiologic Report	Fatalities caused by COVID-19 are mostly concentrated in older age groups who suffer from underlying medical conditions. Dementia considerably increase risk of poor outcome associated with infection.	[10]
Zubair AS	Review	Review summarizing information regarding coronaviruses in the nervous system, the link with potential tissue targets and routes of entry of SARS-CoV-2 into the central nervous system and the range of clinical neurological and psychiatric complications	[14]
Mao L	Case Series	Case series including 214 patients affected by COVID-19 in Wuhan, China. 78 patients (36.4%) had neurologic manifestations. Patients with more severe infection had neurologic manifestations, such as acute cerebrovascular diseases (5 [5.7%] vs 1 [0.8%]), impaired consciousness (13 [14.8%] vs 3 [2.4%]), and skeletal muscle injury (17 [19.3%] vs 6 [4.8%])	[16]
Hascup ER	Expert opinion	Older adults > 65 years of age constitute a high-risk group prone to severe infection and death by COVID-19. BBB deterioration in older adults leaves them more susceptible to neuroinvasion during SARS-CoV-2 infection. After the acute recovery phase, the long-term consequences on accelerated aging and age-related neurodegenerative disorders are unknown and long-term neurological follow-up is needed	[17]
Clarfield AM	Guidelines	Guideline that propose for anyone who fell ill receive active palliative care throughout the course of a COVID-19 infection but especially at the end of life. The very frail, old-old and severely demented should be actively protected from dying on ventilation	[22]

Vergano M	Guidelines	Older frail people affected by COVID-19 are people with higher fatality rate. Palliative care should be always provided when needed	[23]
Wang H	Expert opinion	As recommended by international dementia experts and Alzheimer's Disease International, support for people living with dementia and their caregivers is needed urgently worldwide. In addition to physical protection from virus infection, mental health and psychosocial support should be delivered.	[25]
Yang Y	Expert opinion	People living with dementia are among the most vulnerable population during pandemic. Support for people living with dementia and caregivers is needed urgently worldwide	[26]
Palmer K	Review	COVID-19 outbreak and related infection control measures could have a higher impact on the frail individuals, worsening the condition of patients affected by non-communicable diseases. Specific strategies should be dedicated to this population	[27]
Palmieri L	Epidemiologic Report	Individuals dying with COVID-19 present with high levels of comorbidities, irrespective of age group, but a small proportion of deaths occurs in healthy adults with no pre-existing conditions.	[28]
Gao J	Survey	The prevalence of depression, anxiety and combination of depression and anxiety (CDA) was 48.3% (95%CI: 46.9%-49.7%), 22.6% (95%CI: 21.4%-23.8%) and 19.4% (95%CI: 18.3%-20.6%) during COVID-19 outbreak in Wuhan, China. More than 80% (95%CI:80.9%-83.1%) of participants reported frequently exposed to social media. After controlling for covariates, frequently social median exposure (SME) was positively associated with high odds of anxiety (OR = 1.72, 95%CI: 1.31-2.26) and CDA (OR = 1.91, 95%CI: 1.52-2.41) compared with less SME.	[29]
Tian F	Survey	Survey on 1,060 participants investigated in China. More than 70% of them have moderate and higher level of psychological symptoms specifically elevated scores for obsessive compulsion, interpersonal sensitivity, phobic anxiety, and psychoticism. Those who were of over 50 years old, had an undergraduate education and below, were divorced or widowed, and agricultural workers had significantly more symptoms.	[34]
Chiao CY	Review	A systematic review of twenty-one articles published between 2003 and 2012, concerning caregiver burden in dementia patients. The aim of this review article is to identify the main factors of caregiver burden among the informal caregivers of people with dementia living in the community. Behavioural problems or psychological symptoms were the primary factor of the person with dementia that is associated with caregiver burden.	[35]
Abbatecola AM	Expert opinion	A brief commentary about recent findings related to age-related comorbidities commonly found in advanced age and their percentages in older Italians that have recently died with a COVID-19. Available data from the ISS show that the most common comorbidities observed in all Italians dying with COVID-19 are arterial hypertension (74.7%) and Type 2 Diabetes (30.5%).	[36]
Bostanciklioglu M	Review	During pandemic clinic studies of AD have been stopped to protect the patients. This article suggests that isolating patients with dementia in fully-equipped nursing homes can be a more appropriate exit strategy for the protection of dementia patients and research.	[37]

Geerts H	Guidelines	Clinical trials have been stopped by the COVID-19 pandemic. This report proposes the virtual twin patient approach, based on mechanistic modeling, including physiologically-based pharmacokinetics (PBPKs) and Quantitative Systems Pharmacology (QSP), as a possible innovative way	[40]
Ousset PJ	Expert opinion	Teleconsultation and hospitalization units in which Covid-19 positive patients affected by dementia could be treated, may be two solutions to deal with this unprecedented situation	[41]
Cuffaro L	Expert opinion	During pandemic telemedicine could provide a possible solution for providing cares to people with dementia limiting access to hospitals and personal contacts	[43]
Francisco EM	Guidelines	The European Commission, the European Medicines Agency (EMA) and National Head of Medicines Agencies (HMA) have published a guidance on how to manage the conduct of clinical trials in the context of the coronavirus disease (COVID-19) pandemic.	[44]
Brooks SK	Review	Review of 24 papers about the psychological impact of quarantine. It underlines how the negative quarantine effects, represented by anger and post-traumatic stress symptoms, can be associated with negative determinants such as quarantine duration, infection fears, frustration, boredom, inadequate supplies, inadequate information, financial loss, and stigma with possible long-lasting effects	[47]
Ward CF	Case Series	4 different cases of people who had already received a diagnosis of dementia in which confusion, agitation and disorientation have been the presenting symptom of COVID	[48]
Cawthon P	Expert opinion	COVID-19 sequelae are not well described. Observational studies will be able to describe the before- and after-condition of participants and the effects of the social distancing rules on the health. Such information would help guide the continued clinical management	[49]
Nicola M	Review	COVID-19 pandemic has had a strong social and economic impact all over the world. Social distancing, self-isolation and travel restrictions have led to a reduced workforce across all economic sectors and caused many jobs to be lost.	[50]
Dubey S	Review	Global infection itself multiplied by quarantine to combat COVID-19 applied by nationwide lockdowns produce acute panic, anxiety, obsessive behaviors, hoarding, paranoia, and depression, and post-traumatic stress disorder (PTSD) in the long run. These have been fueled by an “infodemic” spread via different platforms of social media.	[51]
Rajkumar RP	Review	Preliminary evidence suggests that symptoms of anxiety and depression (16-28%) and self-reported stress (8%) are common psychological reactions to the COVID-19 pandemic, and may be associated with disturbed sleep. Symptoms are more common in older population but can affect also children and adolescents.	[52]
Buonsenso D	Survey	The psychological impact of quarantine and economic uncertainty has resulted in the development of anxiety symptoms in more than half of the population that are aggravated by the previous economic state	[53]
Chetterje P	Expert opinion	Work produced in the early stages of the infection in India that denounces an unpreparedness to face the psychological consequences of the pandemic and lockdown in India, which can be aggravated by the stigma of the disease	[54]
Xu X	Survey	In an elderly population in China 25.8% of interviewees showed purchase	[55]

		intention in long-term care insurance (LTCI) in the time before the COVID-2019 outbreak, while this proportion increased to 37.6% after the COVID-2019 outbreak. The emergency had led to an increased concern for death in the elderly population	
Zhu J	Survey	Survey conducted in Gansu, China, including 79 doctors and 86 nurses that demonstrated a prevalence of anxiety of 11% and depression of 46% in doctors and 28% and 43.0% in nurses. Such symptoms were more frequent in women and in those who had already experienced psychological symptoms before the pandemic.	[56]
Lara BB	Original study	40 subjects diagnosed with MCI (20) or mild AD (20) assessed during the month prior to the lockdown, were reevaluated after 5 weeks of social isolation via the neuropsychiatric scale (NPI) and EuroQol- 5D. The total basal NPI score worsened by about 6 points, from 33.75 to 39.05 after confinement, with the appearance of various neuropsychiatric symptoms including apathy and anxiety in subjects with MCI and apathy, agitation and aberrant motor behavior in AD patients.	[57]

Figures



Figure 1

Flow diagram showing the selection process