COVID-19 IN THE MEDITERRANEAN AREA: EPIDEMIOLOGY AND MAIN DISEASE CHARACTERISTICS - A NARRATIVE REVIEW

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ABSTRACT

In December 2019, Chinese researchers identified a novel coronavirus in humans that caused acute respiratory syndrome- officially called coronavirus disease (COVID-19) as of February 11, 2020. At the beginning of the outbreak, the Mediterranean countries seemed to be spared from the health and social disaster happened in China. Unfortunately, the spread of the virus ran faster than forecasts and Italy was unfortunately then followed by Spain, France and other countries in counting many cases and deaths. The World Health Organization declared COVID-19 a pandemic on March 11th, 2020. A retrospective analysis of big data from Google Trends, using an infodemiology approach, shows how internet traffic search on COVID-19 may figure on the spread curve.

The clinical aspects of COVID-19 range from poor or mild symptomatic patients to severe respiratory disease which can quickly lead patients to respiratory failure and admission to intensive care units. Multi-organ involvement and different types of symptoms other than respiratory have been described.

Nowadays the vaccination is still under investigation and there is not a specific treatment approved for COVID–19. While several drugs and therapeutic strategies are currently under investigation and deserve further well-designed, prospective epidemiological and clinical studies with high methodological standards, the literature highlights the role of Chloroquine and its less toxic derivative Hydroxychloroquine in the therapeutical management of COVID-19. Those drugs have been proposed as a potential treatment for COVID-19 and clinical trials are undergoing to evaluate this drug. However have known oxidative properties that could decrease glutathione levels and may cause severe haemolysis in G6PD-deficient patients. Deficient G6PD alleles are distributed worldwide; a conservative estimate is that at least 400 million people carry a mutation in the G6PD gene causing deficiency, the Mediterranean most frequent variant is a class II allele (1-10% of residual activity). With worldwide spread of COVID-19, also in regions with a high prevalence of G6PD deficiency, physicians should be aware of this possible correlation.

Keywords: *COVID-19, mediterranean area, infodemiology, glucose-6-phosphate dehydrogenase (G6PD) deficiency, hydroxychloroquine.*

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Introduction and epidemiology

Since at least December 2019, a cluster of patients affected by with pneumonia of unidentified infectious cause has been reported starting from the city of Wuhan, China. The causative viral pathogen was subsequently traced and identified as the severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2). It is a newly described betacoronavirus, now identified as the etiologic agent of corona virus disease 2019 (COVID-19). Since the recognition of COVID-19, there has been an exponential rise in the number of cases worldwide[(1)].

As of 9 May 2020, the World Health Organization reported more than 3,94 million cases in more than 195 countries. Human-to-human SARS-Cov-2 infection mainly spreads through the respiratory tract, by droplets, respiratory discharges, and direct contact giving reason for the rapid spread of the epidemics[(2-4)]. Nasopharyngeal, sputum and stools rather than blood and urine, are the major shedding routes for SARS-CoV-2.

Cough seems to be aligned with viral shedding in clinical respiratory and faecal specimens. Stronger antibody response is associated with delayed viral clearance and disease severity[(5)].

A study demonstrated how SARS-CoV-2 remained viable in aerosols for more than 3 hours with a reduction in infectious titre from 103.5 to 102.7 TCID50 per litre of air[6]. Concerning the survival of virus on surfaces SARS-CoV-2 a study found that COVID-19 was more stable on plastic and stainless steel than on copper and cardboard, and viable virus was detected up to 72 hours after application to these surfaces, although the virus titre was greatly reduced (from 103.7 to 100.6 TCID50 per millilitre after 72 hours on plastic and from 103.7 to 100.6 TCID50 per millilitre after 48 hours on stainless steel). On copper, no viable SARS-CoV-2 was measured after 4 hours, while on cardboard, no viable SARS-CoV-2 was measured after 24 hours[6].

As recommended by WHO, frequent handwashing, wearing facemasks and keeping at least 2 mt distance between people can be effective measures for prevention[2, 7]. While the incubation period of SARS-CoV-2 was initially reported to lie between 1 to 14 days with a median of 5 to 6 days[3, 8] (7.1 days in a recent meta-analysis[9], it may be longer, being infectious during the latency period.

The existence of large proportions of asymptomatic or minimally symptomatic carriers[10], the absence of any cross-protective immunity from related viral infections[11] and delayed public health response measures had a relevant impact as well[3, 8].

Of note, in the early stages there is an overlap with allergic rhinitis, influenza, other upper respiratory tract infection symptoms, may hide the infection, which only later progress to a clearer clinical pattern of COVID-19.

This infection can cause severe respiratory illness and multi-organ failure, with presentation greatly resembling those of severe acute respiratory syndrome (SARS-CoV-1) and Middle East Respiratory Syndrome (MERS), both caused also by coronaviruses and leading to intensive care unit (ICU) admission and high mortality. Age and the presence of comorbid disease increase the risk for severe disease or death[12]. The severity of COVID-19 in children is less severe as compared to adults, even though those younger than 1 year seem to be at increased risk for severe disease[13].

Current case-fatality rate estimates range from 0.6% to 7.2% by region (overall around 2.3%) and by the time at analysis since the start of the COVID-19 spread, however it seems to be substantially lower than SARS and MERS but higher than that of seasonal influenza (0.1% mortality rate)[12]. Of note, current estimation of COVID-19 case-fatality rate is probably inflated, being altered by the preferential testing of subjects with moderate to severe manifestations, that happened in many healthcare systems for multiple reasons[12, 14].

In fact, insufficient access to testing and intensive care services (secondary to equipment, staff and space shortages) may have contributed to the fatality rate variation, in particular in the first period of COVID-19 epidemics. However, dissimilarities of fatality rate in different countries may depend also on other factors like the density of population, age of population and local healthcare system organization[15].

Moreover, some data collected by the WHO provides evidence that people living in an area with high levels of pollutant are more prone to develop chronic respiratory conditions and suitable to any infective agent. A prolonged exposure to air pollution leads to a chronic inflammatory stimulus, even in young and healthy subjects. The high level of pollution in some regions such as Northern Italy, central Spain, New York city district in the US and Hubei province in China should be considered an additional co-factor of the high level of lethality recorded in those areas[16]. For instance, a well-known air pollutant like Nitrogen dioxide (NO2) (an ambient trace-gas result of both natural and anthropogenic processes) is related to a wide spectrum of diseases such as hypertension, diabetes, heart and cardiovascular diseases and even death. A recent study suggests that there may be a relationship between long-term exposure to NO2 and COVID-19 fatality[17].

In that study, a Sentinel-5P equipment mapped the tropospheric NO2 distribution and the National Centers for Atmospheric Prediction (NCEP) and the National Center for Atmospheric Research (NCAR) reanalysis for evaluating the atmospheric capability to disperse the pollution. The spatial analysis was conducted on a regional scale and combined with the number of death cases taken from 66 administrative regions in Italy, Spain, France and Germany. Results show that out of the 4443 fatality cases, 3487 (78%) were in five regions located in north Italy and central Spain. Additionally, the same five regions showed the highest NO2 concentration combined with downwards airflow which prevent an efficient dispersion of air pollution[17].

These results indicated that the long-term exposure to this pollutant may be one of the most important contributors to fatality caused by the COVID-19 virus in these regions and maybe across the whole world but more studied are needed to clarify this.

Country	Sum of cases, As of 10th may 2020	Sum of deaths	Reported deaths for 100.000 Population
Italy	218268	30395	50,03
Spain	223578	26478	56,07
France	138854	26310	39,3
Croatia	2176	87	2,1
Montenegro	324	9	1,42
Albania	868	31	1,08
Slovenia	1454	101	4,09
Tunisia	1032	42	0,36
Egypt	8964	514	5,22
Malta	490	5	1
Cyprus	892	21	1,8
Turkey	138657	3786	4,61
Israel	16492	254	2,85
Morocco	5910	186	5,16
Lybia	No reliable data	No reliable data	No reliable data
Algeria	5558	514	1,21
Lebanon	845	26	0,37

Table 1: Prevalence of COVID19 in the Mediterranean Area as of 10th may 2020.

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Infodemiology, a powerful resource for COVID-19. The term Infodemiology was first used by Eysenbach to indicate how the use of population health technologies such as the internet can aid with the detection of diseases during an early stage[18]. The previous outbreaks of SARS, Zika Virus, Ebola and MERS highlighted the potential role of infodemiologic approach to detect more details and forecast current or incoming epidemics or pandemics[19].

Mavragani et al. recently published that Google Trends data can assist the tracking of epidemics and outbreaks. This paper underlines how online search traffic data are highly correlated with COVID-19 cases and deaths rates in the examined countries and regions. In particular, this study shows that regions not yet severely affected (e.g. before reaching the peak of COVID-19 cases), exhibited the strongest relationship between Google and COVID-19 data[20].

This may imply that focus should be shifted towards those regions to make full use of what real time data assessment can offer. The latter is crucial for increasing the awareness and responsiveness of local health institutions, which is the most important aspect in management of the current pandemic.

Chronic respiratory diseases and COVID-19

It may be supposed that patients affected by respiratory chronic diseases would be more prone to develop severe pneumonia related to SARS-CoV-2 virus. Zhang et al. reported the clinical characteristics of 140 cases of community acquired COVID-19 in Wuhan, China, with 82 cases classified as non-severe, and 58 as severe[21]. Interestingly, none of them had a medical history positive for allergic disease or asthma. A recently published paper analysed the prevalence of Asthma and COPD as comorbidity in the clinical reports by Chinese clinical centres: both diseases appear to be under-represented among the comorbidities reported for patients with COVID-19, compared with the global burden of disease prevalence estimates of these conditions in the general population. A similar pattern had been reported with SARS-1 infection. Some hypothesis may explain this peculiar epidemiology. One is the rate underdiagnosis of respiratory disease in front of other chronic diseases such as diabetes, particularly in China. The other hypothesis is that therapies used by patients with chronic respiratory diseases can reduce the risk of infection or of developing symptoms leading to diagnosis. The role of viral infections and influenza vaccination in respiratory disease, including asthma, is well known and will deserve further importance in the near future[22, 23].

Glucocorticoid, biological therapies and the relevant possible risk of adverse outcomes in COVID-19 represents a trending topic[24]. It is known that allergic airway inflammation in the lung in asthma, may suppress anti-viral immunity, thus suppressing allergic airway inflammation with a topical steroid or monoclonal antibody such as omalizumab may also improve antiviral immunity[25]. Thus, inhaled steroid treatment or biological treatments should be initiated/continued/increased as clinically suggested, unless a diagnosis of COVID-19 is reached.

Diagnosis of SARS-Cov-2 infection

Clinical and diagnostic strategy for COVID-19 is based on viral nucleic acid detection, mostly in the rhino-pharyngeal swabs or other respiratory tract samples, by Real-time reverse-transcriptase polymerase chain reaction (RT-PCR) tests. Molecular findings are also used for declaring the recovery, currently defined by the negativity of two consecutive swabs taken 24-hours apart on after recovery of symptoms or after 14 days in asymptomatic patients.

Upper respiratory tract samples included rhino-pharyngeal swab (actually the most frequent collected) that has a positive rate of 63% and oropharyngeal swab (most frequently collected at the beginning of pandemic), with estimated positive rate of 32%[26]. Lower respiratory tract sampling has higher sensitivity and bronchoalveolar lavage

(BAL) has a positive rate of 93%. However, it is an invasive and aerosol generating procedure, not easily executable in all centres and for every patient. Another useful lower respiratory tract type of specimen is sputum, with a positive rate found to be of 72%[26]. It is worth noting that several patients with high suspicion of COVID-19 due to clinical and/or radiologic findings, may result repeatedly negative to upper respiratory tract swabs. Later, they may turn out to be positive on swab or BAL testing, therefore suggesting that one may consider patients as infected despite negativity for molecular tests, cognizant that testing should be repeated when appropriate[27, 28].

A factor that influences the positivity rate on molecular testing is the timing of specimen collection, as the viral load (correlated with RT-PCR sensitivity) is maximum in early and progressive stage of disease and decreases during recovering period[28, 29]. Viral load is higher in samples collected from lower respiratory tract compared with oral/rhino-pharyngeal swabs and remains higher in later stage of disease and in SARS CoV-2 pneumonia. Considering low sensitivity of RT-PCR on upper respiratory tract swabs and the need of find asymptomatic patients, molecular diagnosis should be integrated with other tests, like serology.

Serology

Taking into account the limits of molecular diagnosis for SARS-CoV-2 infection and the importance of identification of asymptomatic or patients in the early or pre-symptomatic phase, many efforts were made find reliable serological tests, and in few months many assays have been developed. Molecular diagnosis remains the gold standard for a certain diagnosis of active SARS-CoV-2 infection.

Findings similar to other infectious diseases by coronaviruses have been shown in SARS-CoV-2 infection, where immune system develop antibodies against the pathogen. The main targets of SARS-CoV-2 antibodies are the Internal Nucleocapsid protein (N protein) and Surface Spike Protein receptor-binding domain (RBD, S protein)[30].

Different studies evaluated the kinetics of SARS-CoV-2 antibodies, with respect to symptoms onset[31, 32]. Usually, IgM appear first during infection, but in some cases seroconversion is simultaneous, or IgG appear earlier then IgM (this could be related to a minor sensitivity in IgM detection)[33]. Both IgM and IgG titre increase and reach a peak in the second week after symptoms onset, but starting from third week IgM stop increasing while IgG titre still rise until reaching a plateau after 21th day[32]. According to available evidence, less than half of patients developed antibodies against SARS-CoV-2 within the first week after symptoms onset but starting from the second week antibodies are detectable in around 90% of patients.

Like other laboratory tests SARS-CoV-2 antibodies detection is performed using qualitative or quantitative tests. Qualitative tests, like immunochromatography, give an IgM and IgG positive or negative result, they don't require a laboratory facility and are results are quickly available. Despite many studies shows high sensitivity and specificity for some test[34-36], the urgent market demands led to availability of high quantity of rapid tests, that have been poorly validated and with lot of divergence in sensitivity and specificity. Quantitative tests, like chemiluminescence or immunoassay tests detect and allow the titration of IgM and IgG, those tests are validated and showed a reproducibility of results. A meta-analysis compared different studies about serological tests, finding a high sensitivity and specificity of quantitative tests (respectively 93% and 96-99% for ELISA based test, 90% and 97-98% for CLIA based tests); the same study evidenced a lower sensitivity of rapid tests (estimated around 80%, with specificity similar to other tests), all those results considered both IgM and IgG detection[37].

Serological diagnosis have some different limits, such as poor sensitivity at early stages of infection, despite RT-PCR from upper respiratory tract swabs has better sensitivity in the first week after symptom onset; it also remain unclear if SARS-CoV-2 IgGs may persist for long time after healing and if they have a role in giving a permanent immunity against SARS-CoV-2 preventing re-infection. Considering temporal profiles of antibodies response and molecular detection, serological tests should not be used instead of RT-PCR for diagnosis of SARS-CoV-2 infection but they can integrate the molecular diagnosis in order to select patients negative at first RT-PCR that should repeat the swab if the antibodies are found positive. Serological tests may also have a role in to find asymptomatic subjects or those who had an unnoticed infection and for epidemiological studies.

Clinical features of COVID-19

General remarks

A currently unclear proportion of people infected with the virus SARS-CoV-2 does not develop

symptoms[10]. Of those who develop clinical signs of COVID-19, about 80 to 90% show mild (flu-like) and self-limited, symptoms manifesting as fever, cough and shortness of breath[15], and the others may develop pneumonia due to the tropism for the lung[15]. Some patients with pneumonia may further rapidly turn into a severe respiratory disease, requiring intubation and mechanical ventilation[38].

A recent meta-analysis of available observational studies showed fever (79.1%; 95% CI, 68.0-90.3%), dry cough (58.0%; 95% CI, 42.0-74.0%) and fatigue (29.3%; 95% CI, 23.4-35.3%) as the most common symptoms at the clinical presentation[9]. Symptoms may also include headache, sore throat, loss of smell/taste, abdominal pain and diarrhoea[39].

Among one of the first described cohorts of COVID-19 patients in China, more than 50% developed dyspnea, with a median duration from illness onset to dyspnea of about 8 days, time to ARDS was between 8 to 9 days, to mechanical ventilation and ICU admission was around 10 days[39, 40].

The most common laboratory findings are lymphopenia and/or leukopenia (about 70%) and eosinopenia (about 50%)[21], a drop in albumin and elevated lactate dehydrogenase and ferritin[9].

Olfactory disfunction

Anosmia was shown in a percentage >of 85% of COVID-19 positive patients[41] and could precede the appearance of other symptoms such as cough and fever[42]. The multicentric European study reported that the olfactory dysfunction affected 11.8% of COVID-19 positive patients before the appearance of any other symptom[41]. The anosmia was reported on COVID-19 positive patients in different countries such as Germany, United States, Italy, United Kingdom, and the Iran[43]. To date neither the World Health Organization (WHO) nor the Centers for Disease Control and Prevention identify the anosmia as a screening symptom. In COVID-19 patients olfactory dysfunction is usually not associated with rhinorrhea or nasal obstruction[41]. A previous study suggested that the central nervous system (CNS) could be affected by the coronavirus[44].

Previous studies in animal models indicated that the coronaviruses can enter after intranasal inoculation during breathing, then progressing through the trigeminal and olfactory nerves[45]. These studies in animal models showed that the coronaviruses could induce demyelination and could activate T cell-mediated autoimmune reactions against human central nervous system.

Consequently, the coronaviruses can enter in the central nervous system through the trigeminal and olfactory nerves. Olfactory nerves are in communication with the nasal epithelium and also with the olfactory bulb. The transport in the nerve could be retrograde or antegrade and is mediated by proteins called dinein and kinesin, which could be possible targets of the COVID-19 viruses[46].

Due to the olfactory dysfunction same patients showed dysgeusia[43]. The post-viral olfactory dysfunction is usually considered a common cause of olfactory dysfunction[47], and Deems and colleagues showed that 26% of patients had anosmia after upper respiratory infections or cold with 63% of women affected[48]. A recent study indicated that the 72.6% of COVID-19 positive patients recovered their olfactory function within 8 days after the resolution of the disease[41]. Future studies are necessary in order to evaluate olfaction in COVID-19 positive patients using objective olfactory tests at different stages of the disease.

Neurological manifestations of COVID-19

The neurotropic potential of SARS-CoV-2 has been proposed by Baig et al.[49]. It has been described that SARS-Cov2 uses the angiotensin converting enzyme2 (ACE2) receptor to penetrate inside the cells. ACE2 receptors are expressed by lung type II alveolar cells, enterocytes, arterial and venous endothelial cells and arterial smooth muscle cells in most organs. ACE2 receptors have also been detected over glial cells and neurons, therefore they could be a potential target of COVID-19.

Although the mechanism of penetration of SARS-CoV-2 into the central nervous system needs to be clarified (blood dissemination, upper nasal transcribial route, transneuronal pathway), neurological manifestations have been reported since the start of the pandemic.

A retrospective study that involved 214 patients hospitalized for COVID-19 infection in Wuhan, has reported neurological manifestations in 78 (36.4%) patients. The study distinguished 3 categories of manifestations as involving the central nervous system, the peripheral nervous system and the skeletal muscles[50]. Central nervous system manifestations were reported in 53 (24.8%) patients: dizziness 36 (16.8%), headache 28 (13.1), impaired consciousness 16 (7.5%), acute cerebrovascular disease 6 (2.8%), ataxia 1 (0.5%), seizure 1 (0.5%). Peripheral nervous system manifestations were described in 19 (8.9%) patients: taste impairment 12 (5.6%), smell impair-

ment 11 (5.1%), vision impairment 3 (1.4%), nerve pain 5 (2.3). 23 patients (10.7%) presented muscle skeletal injury. Neurological symptoms were reported in patients with more severe infection and acute cerebrovascular diseases were more frequent[50]. In severe patients, 5 (6%) had stroke.

Older age and underlying cardiovascular or cerebrovascular disease are supposed to be risk factors for secondary cerebrovascular events. Large vessel ischemic stroke has also been reported in patients younger than 50 years of age positive for COVID-19[51]. A French study that involved 64 patients hospitalized for Acute respiratory distress syndrome due to Covid19 showed neurological manifestations in 58 patients. They presented agitation (69%), corticospinal tract signs (67%), and dysexecutive syndrome at discharge (33%).

13 patients presented encephalopathic symptoms and they underwent MRI brain, that revealed leptomeningeal enhancement, perfusion abnormalities and cerebral ischemic stroke[52].

Clinical characteristics of severe COVID-19

Approximately 14-20% of hospitalized patients have more severe disease and are admitted to ICU, 3 to 10% may require intubation, and 2 to 5% die[15].

In a cohort of 548 Chinese patients, older age (>65 years old), hypertension and elevated levels of LDH and D-Dimer were found to be significantly associated with severe disease. Patients diagnosed with severe disease were more likely to experience complications as ARDS (38,3%) , cardiac injury (21,7%), liver disfunction (19,3%), AKI (17,3%), DIC (7,7%), hyperglycaemia (33,2%)[53].

A recent systematic review and meta-analysis shows that shortening the onset-to-admission time favoured COVID-19 related outcomes in terms of Case Severity Rate and Case Fatality Rate[9].

The most common comorbidities were hypertension (19.0%, 95% CI, 13.2-24.9%), followed by diabetes (8.2%, 95% CI, 6.3-10.0%) and cardiovascular diseases (CVD, 2.7%, 95% CI, 1.4-4.1%). Cardiac involvement, either alone or in combination with respiratory failure, was the cause of death in 68/150 patients in a Chinese cohort[54].

Hypertension, diabetes, CVD, cerebrovascular diseases, chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD) were significantly more common in severe cases than non-severe cases ($p<0.05$)[9].

In a population-based case-control study conducted in the Lombardy region of Italy the use of ACE-inhibitors (ACEi) and Angiotensin receptor blockers (ARBs) were more frequent among patients diagnosed with COVID-19 than among controls. However, this association was found for all the other classes of antihypertensive drugs. A multivariate analysis did not find a significative correlation between ACEi and ARBs use and risk of COVID-19, regardless of gender and age; no association was shown with the severity of the disease, as well. The same study revealed higher prevalence of cardiovascular disease in the population affected, for which these drugs are prescribed, and thus explaining the association[55, 56].

Again, a large multicentric study including 8910 patients hospitalized for COVID-19 did not find an association between ACEi and ARBs use and risk of in-hospital death[56].

STEMI and myocardial injury (either as myopericarditis or myocarditis) may be the first clinical manifestation of COVID-19 and the disease can exacerbate a pre-existing cardiac condition such as HF, AF and hypertension[57]. A comparison study between two groups of patients admitted for COVID-19 related Pneumonia to a large hospital in Northern Italy, either with or without pre-existing cardiovascular disease, has shown an increased mortality rate in cardiac patients (26% vs 9%).

Patients who died were more likely to be older and have a history of HF, CAD, CKD and diabetes. Cardiac patients had higher rates of major events, including development of ARDS, VTE, ATE and septic shock. Laboratory abnormalities on admission including elevated levels of plasma troponin, NT-proBNP, D-Dimer and CRP were associated with worse outcomes and were frequently seen in patients with cardiac disease.

Elevated level of CRP, LDH and D-dimer, together with reduced level of lymphocytes count and platelets count were the prominent features of severe cases (all for $P<0.001$)[9]. Lymphocytopenia may play a key role in evolution of the infection to severe disease, due to the lack of regulatory action of T cells and the subsequent uncontrolled release of inflammation mediators leading to multiple organ failure[58].

The temporal profile of laboratory findings was tracked in 33 patients with COVID-19 pneumonia showing that neutrophil count, D-dimers, blood urea, and creatinine levels continued to increase In the non-survivors, and the lymphocyte counts continued to decrease in the same group[26]. Neutrophilia may be related to cytokine storm induced by viral sepsis, coagulation activation could have been related to

sustained inflammatory response, and acute kidney injury could have been related to direct effects of the virus, hypoxia, and shock[59].

Radiologic assessment of COVID-19

COVID-19 can be recognized by either chest Computed Tomography (CT) scan or chest radiography, usually in combination with clinical signs and laboratory testing. The typical CT primary abnormalities of COVID-19 are identifiable event in asymptomatic patients, rapidly evolve from focal unilateral to bilateral multilobar ground-glass opacity (GGO) with a distribution on the peripheral and lower lobes, in the time of 1 to 3 weeks[60, 61].

In association, in particular in severe patients, multiple bilateral lobular and subsegmental areas of consolidation, that may coalesce, are found and may coexist with GGO[21].

The number of lung segments involved is linked to to illness severity. Atypical CT findings may include pleural effusion (around 5%), nodules, and lymphadenopathies (around 13%) and thus would suggest different diagnoses[60].

Abnormal lung findings may be found on CT scans in asymptomatic subjects (usually with less affected lung segments than those symptomatics), and in 56% of patients who had symptoms since ar least 2 days[61].

CT sensitivity seems to be high in patients with positive RT-PCR (86-97% in different case studies) and lower in patients with only constitutional and non-respiratory symptoms (about 50%)[61].

Chest x-ray sensitivity is lower (around 59%[61]), especially for early stages of disease, and do not show progression index. However, traditional radiography is less expensive than CT, and radiographers, especially those portable, are easier to decontaminate and can be used in places where access at CT is limited.

Lung ultrasound has been used as a diagnostic tool, both in the ED and in some countries also in primary care settings. Sensitivity is around 75% in skilled operators and non-obese patients in a very limited number of cases. Nevertheless, point of care ultrasound may play a role in monitoring the progression of the disease and response to treatment through the detection of interstitial lung disease features (B lines and subpleural consolidations) for critical patients, especially those requiring mechanical ventilation[62], and can reduce the exposure risk between infected patients and health-care workers, and help to discern between low-risk and higher-risk patients[63].

Computer-aided diagnostic tools have been developed based on machine learning algorithm, showing the potential to increase diagnostic efficiency[63].

Chest radiography is less sensitive then chest CT, especially for early stages of disease and do not show progression index, however traditional radiography is less expensive then CT, and radiographers, especially those portable, are easier to decontaminate and can be used in places where access at CT is limited. At present, the best imaging strategy remains undefined, CT scanning is usually reserved for patients with an undefined clinical picture, as well as for differential diagnosis[60].

G6PDH deficiency and COVID-19

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an inherited genetic disorder caused by RBCs defects and is associated with haemolytic crisis when patients are exposed to oxidative agents (infections, ingestion of fava beans, drugs). With worldwide spread of COVID-19, also in regions with a high prevalence of G6PD deficiency, physicians should be aware of this possible correlation[64].

Although usually heterozygous women have less severe clinical manifestations than G6PD deficient males, some develop severe acute haemolytic anaemia. Deficient G6PD alleles are distributed worldwide; a conservative estimate is that at least 400 million people carry a mutation in the G6PD gene causing deficiency, the Mediterranean most frequent variant is a class II allele (1-10% of residual activity)[65]. The highest prevalence is reported in Africa, southern Europe, the middle east, southeast Asia and the central and southern Pacific islands.

An acute haemolytic episode in G6PD deficient subjects usually arises when red blood cells undergo oxidative stress triggered by agents such as drugs, infection, or the ingestion of fava beans. G6PD deficiency does not seem to affect life expectancy, quality of life, or the activity of affected individuals. It may have been selected by enhanced resistance to infections, such as malaria, in many areas[66, 67], although no data are yet available with reference to SARS-Cov-2 infection. Several clinical disorders, such as diabetes and myocardial infarction, and strenuous physical exercise, have been reported to precipitate haemolysis in G6PD deficient individuals; however, coexisting infection or oxidant drug exposure can act as main causes.

The role of G6PD deficiency on viral diseases may result from its potential role in oxidative stress

metabolism[68]. G6PD deficiency can represent a challenge during the COVID-19 pandemic, also due to the previous data showing that human coronavirus (HCoV) 229E infection may have an increased susceptibility in G6PD deficiency models[69]. Chloroquine and its less toxic derivative Hydroxychloroquine, have been proposed as a potential treatment for COVID-19 and clinical trials are undergoing to evaluate this drug. Hydroxychloroquine has oxidative properties that could decrease glutathione levels and may cause severe haemolysis in G6PD-deficient patients[70].

Discussion and conclusion

The global outbreak of SARS-CoV-2-induced COVID-19 is pushing many health care systems worldwide close or beyond the limits of their capacity. The key intervention currently viable and proven to decrease the disease spread is the quarantine measures for the general population. The role played by the levels of pollutant may be further investigated. Intensive diagnostics deployment probably contributed to the success of a few Countries in controlling transmission, together with infodemiology and big data analysis, which might offer novel approaches for health interventions during this pandemic.

Furthermore, the identification of patient or population subsets holding specific molecular, pathological and/or clinical features that may benefit from targeted non-pharmacologic and pharmacologic approaches would be a further step in optimizing future strategies. The impact or potential of identifying key symptoms or alterations in asymptomatic or early phase of the SARS-COV-2 infection, together with technology, will have a crucial role in controlling the outbreaks in the near future.

In this regard, more general approaches such as umbrella or network meta-analysis may be useful.

The cornerstone of patient management is based mainly on supportive therapy and on treating the symptoms and trying to prevent respiratory failure and optimal management of the patient by oxygen delivery and invasive and non-invasive ventilation.

Withdrawal of ACEi and ARB drugs despite no evidence of augmented susceptibility to SARS-CoV-2 infection can be harmful, especially in particular populations as those suffering from CHF and kidney disease[71].

A surge in out-of-hospital cardiac arrest has been observed in a 40-days period in coincidence with the Covid-19 outbreak in Northern Italy, with a strong correlation between the cumulative incidence of both conditions. Of those suffering a cardiac arrest 103 out of 362 had suspected or confirmed COVID-19[72]. A big effort will be to understand and learn how to manage with COVID-19 patients or with those at higher potential risk of severe outcomes, such as concomitant chronic immune-mediated or neurological diseases[73].

Several clinical trials of possible treatments for COVID-19 are ongoing, based on diverse strategies including direct antiviral agents, anti-inflammatory and immunomodulatory drugs, anticoagulants and other therapies including the convalescent plasma[74, 75]. Data have been reported on the efficacy of this drug in patients with SARS-CoV-2-related pneumonia with different severity[76], and results of clinical studies led China regulators to include chloroquine in the recommendations for the prevention and treatment of COVID-19 pneumonia[77].

If Chloroquine and hydroxychloroquine will be demonstrated to be the effective for COVID-19 especially in outpatient care programs and/or in the early phase of disease, still needs evidences. Treating COVID-19 with these drugs in G6PD-deficient patients may represent a challenge, and therefore additional precautionary measures to prevent COVID-19 from reaching G6PD-deficient individuals should be taken.

It is acknowledged that infection, inflammation and thrombosis are intertwined mechanisms, and consequently, these highly increased proinflammatory cytokines are believed to be potential targets for biological therapy.

Finally, the overload of different information and input on potential drugs and therapeutic strategies for COVID-19, highlighted the need for well-designed prospective epidemiological and clinical studies with high methodological standards in order to produce valuable scientific evidence on this topic. Indeed, the health community worldwide is called to face off with one of the most terrible pandemics of the last two centuries, with a burden of deaths also between health workers and an unprecedented economic impact. It is desirable to use every modern tool in our hands and share faster the information in order to forecast, manage and improve the COVID-19 management.

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