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Review

Novel Coronavirus – a Challenge in Diagnosing and Timely Treatment, and its Impact on Population Health Status

Pavlina A. Peneva

Clinic of Pneumology and Phthisiatry, St Marina University Hospital, Medical University of Varna, Varna, Bulgaria

Corresponding author: Pavlina Peneva, Clinic of Pneumology and Phthisiatry, St Marina University Hospital, Medical University of Varna, 1 Hristo Smirnenski Blvd., Varna 9000, Bulgaria; E-mail: p.peneva@abv.bg; Tel.: +359 898 780 406

Abstract

In 2019, the world faced another of the potentially deadly viruses affecting humanity. The new virus, COVID-19, was extremely virulent when it first appeared, with aggressive behaviour toward people unprepared at the time to deal with the infection.

Months later, we already know much about its pathophysiology, but new and unknown pathophysiological aspects of the disease are revealed in time. The clinical picture is not unequivocal at times, with symptoms quite unlike those we have previously considered normal in respiratory infections tending to appear. There have been reports of an increase in the frequency of neoplasms or disease progression due to delayed treatment. Treatment of COVID-19 is still a mirage, and people are struggling with the implications for recovery, the health and economic crisis, and the psychological effects of traumatic stress.

Keywords

COVID-19, epidemic, health crisis, pandemic

INTRODUCTION

In 2019, the world faced another of the potentially deadly viruses affecting humanity. The new virus was extremely virulent when it first appeared, with aggressive behaviour toward people unprepared at the time to deal with the infection. In late 2019, an outbreak of respiratory infection was reported in Wuhan, Hubei Province in China. Information reached WHO and a month later, on January 30th, 2020, an epidemic was declared, followed by the COVID-19 pandemic. The virus was officially reported to cause acute respiratory distress syndrome and was identified as SARS-CoV-2. [1-3]

Months later, we already know much about its pathophysiology, but new and unknown pathophysiological aspects of the disease are revealed with time. The clinical picture is not unequivocal at times, with symptoms, utterly different to those we have previously considered normal in respiratory infections, tending to appear. There are many vague points related to the involvement of particular clusters of people undergoing treatment for their chronic diseases with specific medications. There have been reports of an increase in the frequency of neoplasms or disease progression due to delayed treatment. Treatment of COVID-19 is still a mirage and people are struggling with the implications for recovery, the health and economic crisis, and the psychological effects of traumatic stress.

The purpose of this review is to focus on the clinical course of SARS-CoV-2, the management of anti-epidemiological measures in healthcare facilities, and how this could affect the volume and quality of healthcare, assessing the possible adverse consequences.

PENSOFT

EPIDEMIOLOGY

There is a considerable lineage of coronaviruses, but seven of them are known to cause disease in humans. There are various theories about the origin of the new coronavirus SARS-CoV-2. It has been speculated that it originated from the big seafood and exotic animal wholesale market in the local town of Wuhan, but whatever the mechanism of occurrence, the result is right there: the virus causes diseases of varying severity, and in the most severe cases it has the potential to develop acute respiratory distress syndrome and rapid lethal outcome.

Children get sick more easily, with a hospitalization rate of 20%, compared to that of adults – 33%. The many asymptomatic forms of the disease among youngsters and adolescents are extremely worrying, as they are a vast reservoir and source of infection.[4-6]

CLINICAL MANIFESTATION

The clinical presentation of COVID-19 varies from asymptomatic to severe complications, with pneumonia and death. The incubation period varies from 2 days to 14 days after exposure to the virus.[7] The most common complaints include: cough – mostly unproductive, shortness of breath combined with fever, chills, sore throat, muscle aches, headache, and loss of smell. Complete or partial loss of sense of smell has been studied among 64.4% of mildly symptomatic forms of COVID-19 infection.[7,8] Gastrointestinal complaints such as diarrhoea, nausea, fatigue, etc., have been also often reported.[7,10,11]

A study by Wu and McGoogan of 73 314 patients in China reported that the disease in 81% of the patients had a mild clinical course (no pneumonia or a mild form of pneumonia); 14% of the cases experienced severe course of the disease – with hypoxemia, dyspnoea, over 50% of pulmonary involvement within 24 to 48 hours; critically ill were 5% of the cases – with shock, respiratory or multiorgan failure; in 2.3% of the patients, the disease ended lethally.[12]

A retrospective single-centre study in Shanghai reported that the time from the onset of the first complaints to hospitalization was an average of 4 days (2 – 7 days) among the symptomatic forms. Most of them (93.4%) had an elevated body temperature that lasted approx. 10 days. The average duration of hospitalization was 12 days (12 – 20 days). In 65.7% of the patients, radiological changes appeared 7 days after the onset of complaints, and in 94.5% there was an improvement, with reverse dynamics until day 14 of disease. In conclusion, the team reported that most cases were mild[13], and the frequency of asymptomatic patients remained unknown[14].

It is clear that typical clinical manifestations of COVID-19 include fever, throat pain, fatigue, cough, anorexia, diarrhea, and abdominal pain. However, little is known about the fact that patients with COVID-19 had neurologic manifestations. Some patients might come to the hospital with only neurologic manifestation as their presenting symptoms.

In a follow-up study of 214 patients, Ling Mao et al. reported that 36.4% (78 patients) had various neurological manifestations, 58.9% (126 patients) had a mild infection, and 88 (41.1%) had a severe infection. Elderly patients predominated among those with severe COVID-19, but with fewer complaints typical of the disease. Predominant among them were patients with hypertension. However, severe infections were more likely to cause the development of neurological complaints appearing early in the course of the disease (approx. 1 to 2 days from onset to hospitalization). Neurological manifestations included changes in the central nervous system, peripheral nervous system, or musculoskeletal manifestations.

The most common CNS complaints include dizziness, headache, acute cerebrovascular disease, ataxia, and seizure impaired consciousness. Impaired consciousness includes the change of consciousness level such as somnolence, stupor, and coma, or the change of consciousness content such as confusion or delirium.

Abnormalities of peripheral nervous system (PNS) include vision impairment, taste impairment, smell impairment, and nerve pain.[15]

To identify predictors of COVID-19 in the emergency department (ED), researchers analyzed prospectively recorded clinical features for 391 adult patients in an ED in France, who were tested for SARS-CoV-2. Overall, 57.6% of patients tested positive for SARS-CoV-2. The best predictor for ruling in COVID-19 was anosmia (positive likelihood ratio [+LR], 7.6), followed by presence of bilateral B-lines on lung ultrasound (+LR 7.1).[16]

Skeletal muscular injury manifestations may be present as well.

Myocardial involvement is another serious complication of COVID-19 with an expression of elevated troponin levels. It has been observed in over 22% of the intensive care units patients, leading to cardiac arrest in 12% of the patients. The septic status and cytokine storm are considered as a probable cause.[17]

A study by Arentz et al. conducted in Washington, DC reported a 33% incidence of cardiomyopathies.[18]

Patients with COVID-19 have a higher risk of developing venous thromboembolic complications (VTE), the most serious of which is pulmonary thromboembolism. Bowles et al. reported overcoagulation in patients with SARS-CoV-2. They registered prolonged aPTT in 20% of the monitored patients, indicating a deficiency of coagulation factors or the presence of coagulation inhibitors. These could be factor VIII antibodies or antibodies formed in a non-specific way, for example by the formation of lupus anticoagulant, which was present in 91% of patients with prolonged aPTT.[18,19]

Kloka FA et al. studied 184 patients with proven COVID-19 pneumonia admitted to the ICU. They recorded 31% incidence of venous thromboembolic complications in the study patients (95% CI 20 – 41%), all of whom received standard anticoagulant prophylaxis. Of these, 27% (95%

CI, 17–37% or n = 25.81% of the total) experienced complications of pulmonary embolism, and the remaining 3.7% (95% CI, 0–8.2%) developed arterial thrombotic events.[20]

DIAGNOSTICS

The final diagnosis of acute SARS-CoV-2 infection is laboratory-confirmed by the rRT-PCR method. A study by Steenhuysen et al. stated that during the epidemic in China, nasopharyngeal samples were tested by this method at day 1 (max. at day 3) after hospital admission. Test samples were also obtained from sputum, blood, urine, faeces, nasal secretions, bronchoalveolar lavage (BAL). The team reported that the highest percentage of positive results came from the BAL tests (14/15; 93%), followed by those of sputum (75/104; 72%), nasal secretions (5/8; 63%), brush biopsy (6/13; 46%), pharyngeal secretion (126/398; 32%), faeces (44/153; 29%), blood (3/307; 1%) and urine (0/72; 0%) **(Table 1)**. They indicated that nasal samples contained the highest amount of virus, but less than that in the lower respiratory tract.[21]

Table 1. RT-PCR – a primary and preferred method for diagnosing COVID-19

Method	Test Samples	N	Positive results
rRT-PCR	BAL tests	14/15	93 %
	Sputum	75/104	72 %
	Nasal secretions	5/8	63 %
	Brush biopsy	6/13	46 %
	Pharyngeal secretion	126/398	32 %
	Faeces	44/153	29 %
	Blood	3/307	1 %
	Urine	0/72	0 %

WHO recommendations indicate that in the event of negative PCR results of samples from the upper respiratory tract, and in case of clinical suspicions of SARS-CoV-2, lower respiratory tract material should be tested.[21,22] Furthermore, the requirement of consecutive 24-hour tests in case of a negative first result was indicated in the follow-up study of Xiao, in which a small percentage of patients (11.4%) remained false-negative of the second result, and about 5% of the cases maintained negative results of the third test, although they were ill.[23]

Another study by the same team, regarding positivity and duration of infection, noted that at week 1, all patients were 100% positive, at week 2 – 89.3%, at week 3 – 66.1%, at week 4 – 32.1%, at week 5 – 5.4%, and at week 6 – 0% **(Fig. 1)**.

Moreover, the researchers have established that prolonged virus retention is observed in older patients and diabetics.[24] In some cases, after recovery, the results were positive after two negative previous ones, due to the relapse of the disease.[25,26]

Monitoring antibody titer for COVID-19, various teams identified the presence of IgM a few days after infection, and IgG appeared days later.[27,28] IgM antibody can be produced within 5–7 days and is most useful for determining recent infection, while IgG antibody can be produced within 9-10–15 days and may remain detectable for months or years. Serological detection tests have specificity of 83%-100%, and sensitivity of 60%-83% according to the type of the test.

IgM-ELISA test, performed by Guo et al., obtained positive results in 93% of the cases with typical clinical, epidemiological and radiological data for COVID-19, despite the negative PCR results.[28]

Along with the above-mentioned tests confirming the infection, there are some specific deviations of certain laboratory parameters used in practice. Leukopenia or leukocytosis with or without early-stage lymphopenia is among the
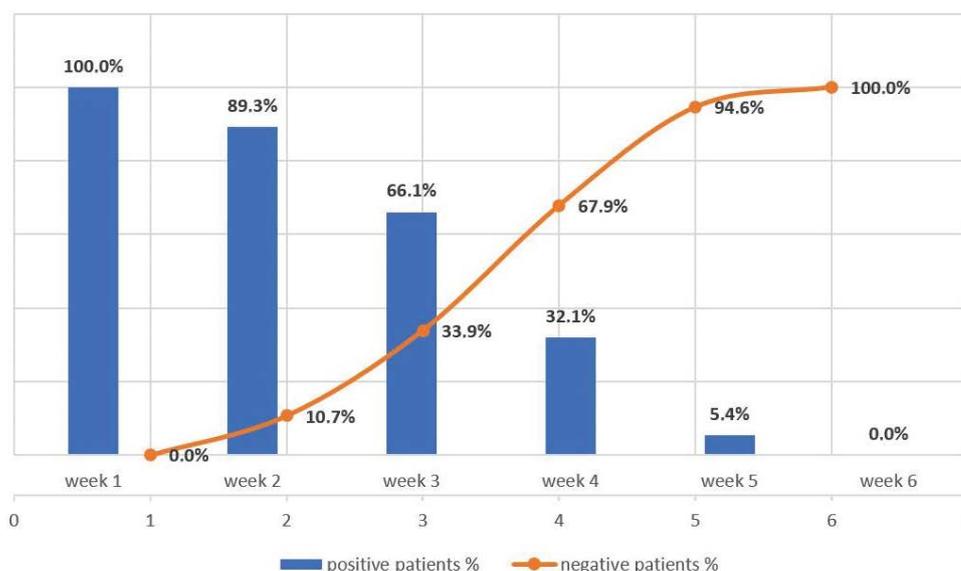

Figure 1. Positivity and duration of COVID-19.

most common abnormalities.[15] Lymphopenia is observed in severe cases, with involvement of the central nervous system, suggesting serious immunosuppression. High D-dimer levels, as well as increased ferritin levels, are more common in severe cases.[29]

Elevated troponin levels in some patients were associated with myocardial damage.[30] Elderly patients with neutrophilia, and elevated LDH and D-dimer levels, had a higher risk of acute respiratory distress syndrome (ARDS) and death, according to a follow-up study of Wu et al.[31] Deviations in SC, LDH, ASAT, ALAT values were a conceivable expression of muscle or liver involvement.[15]

Last but not least, conventional chest radiography and CT have a crucial role in determining the severity of inflammation and lung involvement. Sometimes additional imaging is recommended to clarify complications, considering the wide differential diagnosis.

COVID-19 diagnostics and treatment issues, and impact of the epidemic on the population health status in upper-middle and high-income countries

The review of the clinical picture of COVID-19 shows how difficult it can sometimes be to identify the disease and its complications. Knowledge of the above is essential; therefore, attention to detail of the patient's history is crucial. Atypical clinical presentation and insufficient clinical evaluation pose a hazard. The SARS-CoV-2 outbreak has put the world and especially us doctors to the test. Health systems of all countries have been tested like never before, and health workers have risked their lives facing the first-line challenge of tackling the pandemic.

Hospital admission, medical care and complications in patients with COVID-19

Hospitals and the rest of the health facilities were most involved, and they all had to adjust to the pandemic in a short time. Changes were required in the admission procedures and caring for the sick, regardless of the reason for their hospital visit. At the time, this created substantial organizational problems, and consequences for today's actions.

Unfortunately, we have to mention the delayed care of patients with various other emergencies and acute conditions. All patients are filtered for a survey and/or COVID-19 test. There is no typical clinical picture, but the listed symptoms can provide information about the disease. Something else, changes in the sense of smell have been rarely enquired after, while they could be an essential indication, especially in neurological forms, as well as signalling of the disease.

The review of SARS-CoV-2 clinical picture occasionally shows a set of vague conditions that can be misleading and result in delayed detection of serious complications. Our observations show that once admitted to a hospital, patients with SARS-CoV-2 in addition to being isolated,

might delay their complaints as hospital staff does not visit them as often as they used to in the times before the epidemic. Frequently, some of the patients' complaints are underestimated and/or are associated with viral infection or pneumonia. However, differential diagnosis can sometimes be too broad: conditions from mild malaise to delirium, coma, thrombotic complications, and manifestations of heart failure due to viral myocarditis or other complicated cardiac pathology directly related to cardiac death.

Testing of patients with COVID-19

Timely imaging and instrumental examinations of suspected or SARS-CoV-2 infected patients happens to be a serious problem in hospitals. Nearly all medical institutions have reorganized their services. Same is true for the diagnostic centres. In most hospitals, mainly in the low-middle and upper-middle-income countries, there is no possibility of separated corridors and rooms with designated equipment (CT, MRI), which requires waiting for the 'clean' flow of patients, after which those with COVID-19 are allowed. This can often take hours and delay necessary treatment, which is crucial to avoid complications in which the response time is valuable, with impact on the consequences, disability and mortality.

Effect of crisis in health systems and society on polymorbidity, oncological diseases and their complications

Fear of virus spread necessitated cancellation of planned surgical interventions and tests, which affected the quality of medical care. Most patients scheduled for treatment or those with exacerbations of chronic diseases did not seek medical attention for fear of becoming infected or were postponed in time due to anti-epidemic measures. There are an increasing number of follow-up studies stating that COVID-19 is the cause of delayed diagnosis, accelerated course or recurrence of neoplasms and as a result – rise in the mortality related to this pathology.[32]

An increase in cardiovascular complications, mainly due to delayed treatment, has been observed as well. The number of people with mental health problems is growing as a result of the 'locked-in' lifestyle and social isolation – frequency of depression, fear and aggression increases. We can tell that in addition to affecting the economy and the quality of medical care, COVID-19 has its implications on the general physical and mental health of people, sick and healthy individuals alike. New trends in the overall morbidity are likely to come out, related to the psychological impact of the pandemic on the population of the upper-middle-income and high-income countries.

The impact of COVID-19 on low-income and low-middle-income countries is still unknown. Furthermore, COVID-19 may be devastating for Sub-Saharan Africa region, which has borne the brunt of infectious diseases, including tuberculosis, malaria and AIDS.[33]

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P. Peneva

Новый коронавирус – проблема диагностики и своевременного лечения и его влияние на состояние здоровья населения

Павлина А. Пенева

Клиника пневмологии и фтизиатрии, УМБАЛ „Св. Марина“, Медицинский университет – Варна, Варна, Болгария

Адрес для корреспонденции: Павлина А. Пенева, Клиника пневмологии и фтизиатрии, УМБАЛ „Св. Марина“, Медицинский университет – Варна, бул. „Христо Смирненски“ №1, 9000 Варна, Болгария; E-mail: p.peneva@abv.bg; Тел.: +359 898 780 406

Резюме

В 2019 г. мир столкнулся с ещё одним из потенциально смертельных вирусов, поражающим человечество. Новый вирус – COVID 19 – был чрезвычайно опасен в начале своего появления и имел агрессивный характер по отношению к людям, не подготовленным в то время к борьбе с инфекцией.

За прошедшие месяцы мы уже много узнали о его патофизиологии, но со временем открываются новые патофизиологические аспекты. Клиническая картина иногда бывает неоднозначной, симптомы сильно отличаются от тех, которые ранее считались нормальными при респираторных инфекциях. Поступали сообщения об увеличении частоты новообразований или развитии болезни из-за несвоевременного лечения. Лечение COVID 19 всё ещё остаётся миражом, и люди борются с последствиями выздоровления, кризисом здравоохранения и экономическим кризисом, а также с психологическими последствиями травматического стресса.

Ключевые слова

COVID-19, эпидемия, кризис здравоохранения, пандемия