Saudi Arabia	3,651	47	1.3%	0.14
Slovenia	1,160	45	3.9%	2.18
Bosnia and Herzegovina	901	36	4.0%	1.08
San Marino	344	34	9.9%	100.64
Thailand	2,473	33	1.3%	0.05
North Macedonia	711	32	4.5%	1.54
Moldova	1,438	29	2.0%	0.82
Bangladesh	424	27	6.4%	0.02
Andorra	601	26	4.3%	33.76
Bulgaria	635	25	3.9%	0.36
Tunisia	671	25	3.7%	0.22
South Africa	2,003	24	1.2%	0.04
Estonia	1,258	24	1.9%	1.82
Burkina Faso	443	24	5.4%	0.12
Albania	416	23	5.5%	0.80
Honduras	382	23	6.0%	0.24
Lithuania	999	22	2.2%	0.79
Croatia	1,495	21	1.4%	0.51
Lebanon	609	20	3.3%	0.29
Congo (Kinshasa)	215	20	9.3%	0.02
Belarus	1,981	19	1.0%	0.20
Bolivia	268	19	7.1%	0.17
United Arab Emirates	3,360	16	0.5%	0.17
Afghanistan	521	15	2.9%	0.04
Cuba	564	15	2.7%	0.13
Armenia	937	12	1.3%	0.41
Cameroon	820	12	1.5%	0.05
Diamond Princess	712	11	1.5%	nan
Niger	438	11	2.5%	0.05
Azerbaijan	991	10	1.0%	0.10
Cyprus	595	10	1.7%	0.84
Kazakhstan	812	10	1.2%	0.05
Venezuela	171	9	5.3%	0.03

Mauritius	318	9	2.8%	0.71
Bahamas	42	8	19.0%	nan
Trinidad and Tobago	109	8	7.3%	0.58
Iceland	1,675	7	0.4%	1.98
Singapore	2,108	7	0.3%	0.12
Kosovo	250	7	2.8%	0.38
Nigeria	305	7	2.3%	0.00
Kenya	189	7	3.7%	0.01
Mali	87	7	8.0%	0.04
Uruguay	473	7	1.5%	0.20
Jordan	372	7	1.9%	0.07
Sri Lanka	190	7	3.7%	0.03
Bahrain	925	6	0.6%	0.38
El Salvador	117	6	5.1%	0.09
Qatar	2,512	6	0.2%	0.22
Ghana	378	6	1.6%	0.02
Guyana	37	6	16.2%	0.77
Paraguay	129	6	4.7%	0.09
Taiwan*	382	6	1.6%	0.03
Congo (Brazzaville)	60	5	8.3%	0.10
Kyrgyzstan	298	5	1.7%	0.08
Liberia	37	5	13.5%	0.10
Barbados	67	4	6.0%	1.40
Jamaica	63	4	6.3%	0.14
Tanzania	32	3	9.4%	0.01
Togo	76	3	3.9%	0.04
Oman	484	3	0.6%	0.06
Latvia	612	3	0.5%	0.16
Guatemala	126	3	2.4%	0.02
Georgia	234	3	1.3%	0.08
Ethiopia	65	3	4.6%	0.00
Cote d'Ivoire	444	3	0.7%	0.01
Costa Rica	558	3	0.5%	0.06

Burma	27	3	11.1%	nan
Uzbekistan	624	3	0.5%	0.01
Zimbabwe	13	3	23.1%	0.02

For the 10 countries most affected by COVID-19 worldwide, the bars in the f show the number of deaths either per 100 confirmed cases (observed case-fatality ratio) or per 100,000 population (this represents a country's general population, with both confirmed cases and healthy people). Countries at the top of this figure have the most deaths proportionally to their COVID-19 cases or population, not necessarily the most deaths overall.

The diagonal lines on the **Figure 2** correspond to different case fatality ratios (the number of deaths divided by the number of confirmed cases). Countries falling on the uppermost lines have the highest observed case fatality ratios. Points with a black border correspond to the 10 most affected countries by COVID-19 worldwide, based on the number of deaths. Hover over the circles to see the country name and a ratio value. Use the boxes on the top to toggle between: 1) mortality per absolute number of cases (total confirmed cases within a country); and mortality per 100,000 people (this represents a country's general population, with both confirmed cases and healthy people).

PATHOPHYSIOLOGY

CoVs are the enveloped, positive-stranded RNA viruses with nucleocapsid. For addressing the pathogenetic mechanisms of SARS-CoV-2, its viral structure and genome should be considered. In CoVs, the genomic structure is organized into a +ssRNA of approximately 30 kb in length, which is the biggest identified RNA viruses, with a 3′-poly-A tail and 5′-cap structure. Starting from viral RNA, the synthesis of polyprotein 1a/1ab (pp1a/pp1ab) in the host is realized. Transcription works through the replication-transcription complex (RCT) organized into the double-membrane vesicles and synthesis of the subgenomic RNAs (sgRNAs) sequences. It should be noted that transcription terminates at the transcription regulatory sequences, located between the so-called open reading frames (ORFs) that work as the templates to produce the sub-genomic mRNAs. In atypical CoV genome, at least six ORFs can be present. Among these, a frame-shift between ORF1a and ORF1b guides the generation of both pp1a and pp1ab poly-peptides that have been processed by the virally encoded chymotrypsin-like protease (3CLpro) or the main protease (Mpro), as well as 1 or 2 papain-like proteases for producing 16 non-structural proteins (nsps). Apart from ORF1a and ORF1b, other ORFs encode for the structural proteins, including membrane, spike, nucleocapsid proteins, envelope [1] and accessory proteic chains. Various CoVs present the special accessory and structural proteins translated by the dedicated sgRNAs.

According to the analyses, pathophysiology, virulence mechanisms of CoVs and SARS-CoV-2 are linked to the function of nsps and structural proteins. For instance, research emphasized that nspcan block the host innate immune response [7]. Among functions of structural proteins, the envelope has a crucial role in the virus pathogenicity as it promotes viral assembly and release. However, many of these features (e.g., those of nsp 2 and 11) have not yet been described. Among the structural elements of CoVs, there is the spike glycoproteins composed of two subunits (S1 and S2). Homo-trimers of S proteins contain the spikes on the viral surfaces, guiding the link to the host receptors [8]. Moreover, in SARS-CoV-2, the S2 subunit, which contains a fusion peptide, a transmembrane domain, and cytoplasmic domain, is highly conserved. Thus, it could be a target for antiviral (anti-S2) compounds. On the contrary, the spike receptor-binding domain presents only a 40% amino acid identity with other SARS-CoVs. Other structural elements on which the research should necessarily focus are the ORF3b that has no homology with that of SARS-CoVs and a secreted protein (encoded by ORF8), which is structurally different from those of SARS-CoV. In the international gene banks such as GenBank, researchers have published several Sars-CoV-2 gene sequences. This gene mapping is of fundamental importance so that it allows researchers to trace the phylogenetic tree of the virus and, above all, the recognition of strains that differ according to the mutations. Based on a recent research, a spike mutation, which probably occurred in the late November 2019, triggered jumping to humans. In particular, Angeletti et al. [9] compared the Sars-Cov-2 gene sequence with that of SARS-CoV. They analyzed the transmembrane helical segments in the ORF1ab encoded 2 (nsp2) and nsp3 and found that position 723 presents a serine instead of a glycine residue, while the position 1010 is occupied by proline instead of isoleucine. Therefore, the issue of viral mutations is key for explaining the potential disease relapses. Hence, some studies will be needed to determine the structural characteristics of SARS-COV-2 that focus on the pathogenetic mechanisms. Compared to SARS, initial clinical data showed less extra respiratory involvement, although it is not possible to draw definitive clinical information due to the lack of extensive data.

HISTOPATHOLOGY

Tian et al. [10] reported histopathological data obtained on the lungs of two patients who underwent lung lobectomies for adenocarcinoma and retrospectively found their infection at the time of surgery. Apart from the tumors of the lungs of

both 'accidental' cases showed edema and important proteinaceous exudates as large protein globules. The authors also reported vascular congestion combined with inflammatory clusters of fibrinoid material, multinucleated giant cells, and hyperplasia of pneumocytes.

HISTORY AND PHYSICAL CHARACTERISTICS

The clinical spectrum of COVID-19 varies from asymptomatic or paucisymptomatic forms to the clinical conditions characterized by respiratory failures, which necessitates mechanical ventilation as well as supports in an intensive care unit (ICU), to multiorgan and systemic manifestations in terms of sepsis, multiple organ dysfunction syndromes (MODS), and septic shock. According to one of the first reports on the disease, Huang et al. [11] illustrated that patients (n=41) suffered from fever, malaise, dry cough and dyspnea. In addition, the chest computerized tomography (CT) scans showed pneumonia with abnormal findings in all cases. About a third of those (13: 32%) required ICU care and 6 (15%) fatal cases have been reported. Moreover, Li et al.'s [5] case study reported in the New England Journal of Medicine (NEJM) on January 29, 2020 encapsulated the first 425 cases recorded in Wuhan. According to the data, the patients' median age has been 59 years in the range of 15 to 89 years. These researchers reported no clinical cases in children >15 years of age. Furthermore, no significant gender differences (56% male) have been observed. Clinical and epidemiological data from the Chinese CDC and with regard to 72,314 case records (confirmed, suspected, diagnosed, and asymptomatic cases) have been shared in the Journal of the American Medical Association (JAMA) (February 24, 2020) and provided an important illustration of the epidemiologic curve of the Chinese outbreak [12]. There have been 62% confirmed cases, including 1% of cases that have been asymptomatic, but laboratory-positive (viral nucleic acid test). Consequently, the overall case-fatality rate (on the confirmed cases) equaled 2.3%. As a result, the fatal cases have been primarily observed in the elderly patients, in particular, those aged ≥80 years (about 15%) and 70 to 79 years (8.0%). Approximately half (49.0%) of the critical patients and affected by the pre-existing comorbidity like cardio-vascular disease, chronic respiratory disease, oncological diseases, and diabetes died due to the disease. While 1% of the patients aged 9 years or younger and no fatal cases occurred in this group.

It is notable that the authors of the Chinese CDC report divided the clinical manifestations of the disease by their severity:

- Mild disease: Non-pneumonia and mild pneumonia that occurred in 81% of cases.

- Severe disease: Dyspnea, respiratory frequency ≥ 30/min, and blood oxygen saturation. (SpO2) ≤ 93%, PaO2/FiO2 ratio [the ratio between the blood pressure of the oxygen (partial pressure of oxygen, PaO2) and the percentage of the oxygen supplied (fraction of the inspired oxygen, FiO2)] < 300, and/or lung infiltrates > 50% during 24-48 h that occurred in 14% of cases.

- Critical disease: Septic shock, multiple organ dysfunction (MOD) or failure (MOF) and respiratory failure that occurred in 5% of cases [12].

Data obtained from the reports and directives provided by the health policy agencies allowed the division of the clinical manifestations of the disease according to the severity of the clinical pictures. It has been found that COVID-19 may exhibit with the mild, moderate, or severe disease. Among these serious clinical manifestations, there are acute pneumonia, sepsis, septic shock and ARDS. On the one hand, clinical course of the disease seems to predict a favorable trend in the majority of patients so that a sudden worsening of the clinical conditions with the rapidly worsening respiratory failure and MOD/MOF has been observed after about a week. Finally, the criteria of the severity of the respiratory insufficiency and diagnostic criteria of sepsis and septic shock can be used as a reference [13].

Uncomplicated (mild) illness

These patients usually exhibit symptoms and signs of an upper respiratory tract viral infection, including mild fever, cough (dry), nasal congestion, headache, malaise, sore throat and muscles pain, or malaise. However, symptoms of a more serious disease, such as dyspnea, have been not observed. Compared to the previous HCoV infections, it is a challenge to find the non-respiratory symptoms such as diarrhea.

Moderate pneumonia

Moreover, respiratory symptoms such as cough and shortness of breath (or tachypnea in children) are reported without signs of severe pneumonia.

Severe pneumonia

Fever is associated with severe dyspnea, respiratory distress, tachypnea (>30 breaths/min), and hypoxia (SpO2<90% on room air). However, the fever symptom must be interpreted carefully because it can be moderate or even absent even in the serious or acute forms of illness. Cyanosis can occur in children. In this definition, the diagnosis is clinical, and radiologic imaging is used for excluding complications.

Acute Respiratory Distress Syndrome (ARDS)

It is widely accepted that diagnosis requires clinical and ventilatory criteria. This syndrome suggests a serious new-onset respiratory failure or for worsening of an already identified respiratory picture. Therefore, different forms of ARDS are distinguished based on the degree of hypoxia. The reference parameter is the PaO2/FiO2:

- Mild ARDS: 200 mmHg<PaO2/FiO2 ≤ 300 mmHg. In not-ventilated patients or in those managed through non-invasive ventilation (NIV) by using positive end-expiratory pressure (PEEP) or a continuous positive airway pressure (CPAP) ≥ 5 cm H2O.

- Moderate ARDS: 100 mmHg<PaO2/FiO2 ≤ 200 mmHg.

- Severe ARDS: PaO2/FiO2≤100 mmHg.

Notably, in case of unavailability of PaO2, a ratio of SpO2/FiO2 ≤ 315 would suggest ARDS.

In addition, chest imaging includes chest radiograph, lung ultrasound and CT scan, demonstrating the bi-lateral opacities (lung infiltrates >50%), which would not be thoroughly illustrated by lobar, lung collapse, or effusion. Although in some cases, the clinical scenario and ventilator data could indicate pulmonary edema, the primary respiratory origin of the edema is proven after excluding cardiac failure or other causes such as fluid overload. Hence, echocardiography can be helpful for this purpose.

Sepsis

In accordance with the International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), sepsis represents a very dangerous organ dysfunction induced by the dysregulated host responses to the suspicious or proven infections, with organ dysfunction [14]. On the other hand, clinical pictures of patients affected by COVID-19 and sepsis are particularly serious, characterized by a wide range of signs and symptoms of multiorgan involvement. These symptoms include respiratory manifestations such as severe dyspnea and hypoxemia, renal impairment with the reduced urine output, tachycardia, altered mental status and functional alterations of organs expressed as the laboratory data of hyperbilirubinemia, acidosis, high lactate, coagulopathy, and thrombocytopenia. It is notable that the Sequential Organ Failure Assessment (SOFA) score is the reference for the evaluation of multiorgan damage and the related prognostic significance, which anticipates ICU mortalities on the basis of the lab outputs and clinical information [15]. Finally, validity of a pediatric version of the score has been confirmed [16].

Septic shock

In this scenario, which is associated with the increased mortality, circulatory and cellular/metabolic abnormalities such as the levels of serum lactate higher than 2 mmol/L (18 mg/dL) have been reported. Since patients usually suffer from the persisting hypotension despite volume resuscitation, it is necessary to administer vasopressors for maintaining a mean arterial pressure (MAP) higher than or equal to 65 mmHg.

TREATMENT AND MANAGEMENT

According to the studies, no specific antiviral treatment for COVID-19 has been recommended and, no vaccine is currently available. Treatment is symptomatic and oxygen therapy represents a main therapeutic intervention for patients suffering from severe infection. In addition, mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing the septic shock. With regard to the early in vitro studies, chloroquine blocked COVID-19 infection at low micro-molar concentration, with a half-maximal effective concentration (EC50) of 1.13 μM and a half-cytotoxic concentration (CC50) higher than 100 μM [17]. Therefore, authors quickly conducted some subsequent clinical trials in China for testing the effectiveness and safeness of chloroquine or hydroxychloroquine for treating the COVID-19 related pneumonia in higher than ten hospitals in Jingzhou, Wuhan, Beijing, Guangzhou, Chongqing, Ningbo and Shanghai [18]. Furthermore, outputs obtained from above 100 patients revealed the superiority of chloroquine phosphate over the control treatment for inhibition of exacerbated pneumonia, which ameliorated the lung imaging results, promoted a virus-negative conversion and shortened the disease course based on the news briefing. Consequently, authors observed serious bad reactions to chloroquine phosphate in the above patients. With regard to the outcomes, a conference has been held on February 15, 2020 and people participating in the conference like the experts from stateas well as regulatory authorities and organizers of the clinical trials made consensus of the potential activities of chloroquine phosphate against COVID-19. This medicine has been advised to be included in the next version of Guidelines for Prevention, Diagnosis, and Treatment of Pneumonia Induced by COVID-19 released by the National Health Commission of the People's Republic of China. Chloroquine has been considered to be utilized for the prevention and treatment of malaria and has been confirmed as an effective drug as one of the anti-inflammatory agents to treat lupus erythematosus and rheumatoid arthritis. However, investigations illustrated its potential wide spectrum antiviral activity *via* enhancing the endosomal pH needed for virus and cell fusion and intervening with glycosylation of the cellular receptors of SARS-CoV [19,20] The antiviral and anti-inflammatory activity of chloroquine can demonstrate its potential efficiency to treat the patients suffering from COVID-19 pneumonia. In addition, chloroquine has been considered one of the inexpensive and safe drugs utilized for above 70 years [21]. Regarding crucial clinical demands, chloroquine phosphate has been advised for treating the COVID-19-related pneumonia in larger populations in the future. In order to diagnose COVID-19, though RT-qPCR is specific, its false-negative rate could not be neglected due to very bad effects of the missed diagnosis. Therefore, multiple clinicians introduced CT scan as a crucial auxiliary

diagnostic approach due to its higher sensitivity. In addition, the combined frequent RT-qPCR tests and chest CT scans could be beneficial for people with highly clinical suspected SARS-CoV-2 infections with negative RT-qPCR screening. In particular, high-resolution CT (HRCT) for the chests would be required to initially diagnose and evaluate the disease acuteness in the patients affected by SARS-CoV-2. In this regard, numerous investigations examined the CT images of the patients' chests infected with SARS-CoV-2. Characteristic CT images showed consolidative pulmonary opacities as well as bi-lateral pulmonary parenchymal ground-glass, occasionally with a peripheral lung distribution and rounded morphology. It is notable that the lungs' involvement with a peripheral predominance has been observed in patients with MERS-CoV and SARS-CoV infections. Moreover, chests CTs indicated the disease progression with the ground-glass opacity and consolidation that is the same as the SARS-CoV-2 infection. It has been found that the CT scans showed a very clinical diagnostic significance for COVID-19, specifically in a high prevalence area of SARS-CoV-2 infections. Nonetheless, CT scans suffer from a number of caveats like in-distinguishability from other viral pneumonia and hysteresis of abnormal CT imaging. With regard to the disadvantage of the newly applied nucleic acid detection and CTs to diagnose COVID-19, it is necessary for the clinical laboratories to utilize a number of immunological detection kits, which immediately targeted the viral antibodies or antigens. As a result, a number of companies in the field devised and pretested POCT of IgM/IgG and ELISA kits for SARS-CoV-2 and showed greater rate of detection in comparison to the nucleic acid detection, though any products or articles have been not yet reported. On the other hand, sensitivity of SARS-CoV N-based IgG ELISA (94.7%) has been considerably greater than that of the SARS-CoV S-based IgG ELISA (58.9%); however, SARS-CoV-2 IgG/IgM sensitivity should be investigated. Ultimately, it is necessary to develop additional specific and sensitive auxiliary techniques to diagnose COVID-19.

DIFFERENTIAL DIAGNOSIS

According to the analyses, symptoms of the early stages of the disease are non-specific and thus differential diagnosis should include the possibility of a wide range of infectious and non-infectious (e.g., vasculitis and dermatomyositis) common respiratory disorders.

- Adenovirus,

- Influenza,

- Human metapneumovirus (HmPV),

- Parainfluenza,

- Respiratory syncytial virus (RSV), and

- Rhinovirus (common cold)

Moreover, for the suspected cases, rapid antigen detection and other investigations should be adopted for evaluating common respiratory pathogens and non-infectious conditions.

DETERRENCE AND PATIENT EDUCATION

Patients and families should receive the following instructions:

➢ Persons should avoid the close contacts with the individuals having acute or severe respiratory infection.
➢ People should wash their hands regularly, in particular, following the contacts with sick persons or the respective environments.
➢ People should stop the unprotected contacts with farms or wild animals.
➢ Persons having the symptoms of serious airway infections should keep their distances, cover coughing or sneezing with disposable clothes and tissues, and wash frequently their hands.
➢ Moreover, immunocompromised patients should avoid public exposure and public gatherings. If an immunocompromised individual must be in a closed space with multiple individuals present, such as a meeting in a small room; masks, gloves, and personal hygiene with antiseptic soap should be undertaken by those in close contact with the individual. In addition, prior room cleaning with antiseptic agents should be prioritized and performed before exposure. However, with regard to the dangers involved to these individuals, exposure should be avoided unless a meeting, group event, and the like is a true emergency.
➢ Strict personal hygiene measures are necessary for prevention and control of this infection.

CONCLUSION

According to the analyses, incidence and development of SARS-CoV-2 are depended on the interactions between virus and humans' immune systems. In fact, viral parameters included the kind of virus, viral load and titer, viability of the virus *in vitro* and mutation. Moreover, immune system parameters of humans included age, genetics (e.g., HLA genes), gender, neuro-endocrine-immune regulation, physical status and nutrition. Therefore, all of the mentioned parameters play a role in of one person would be infected with the virus and duration and severity of the disease, as well as reinfection or not. However, during the initial phases of the epidemic, precise diagnosis contributes to the control of the disease spread or expansion. Hence, development of a novel, safe, precise, rapid and easy technology should be prioritized to detect SARS-CoV-2. In addition, doctors would, physicians would deliberately apply interventions in both parameters for developing them into a path helpful to human health so that they would assist the fast recovery of

the patients. Nonetheless, it should be kept in mind that medical interventions could obtain a 100% curative effect.

AUTHORS' CONTRIBUTION

We declare that the present research has been conducted by the researchers mentioned in the paper and each liability related with the claims on the paper contents has been up the researchers.

ETHICAL APPROVAL

Researchers of the present research did not involve any investigations with the human participants or animals.

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