https://doi.org/10.52418/moldovan-med-j.65-2.22.08
UDC: 616.98:578.834.1

Factors to consider when assessing the severity of COVID-19

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Manuscript received September 26, 2022; revised manuscript November 23, 2022; published online December 20, 2022

Abstract

Background: Analysis and evaluation of the multitude of parameters that impact and mirror clinical evolution of COVID-19 infection. Narrative literature review type of study. Bibliographic search of the PubMed database, applying the keywords: "SARS-CoV-2", "COVID-19", "risk score", "laboratory parameters", "pathophysiology", "cytokine storm", "imaging evaluation", "outcomes", "clinical evolution", which were combined with each other. There were selected English-language publications, in extenso, published in recognized journals from March 2020. Priority in the analysis was given to articles of critical synthesis of literature, randomized studies, those with large samples of patients. One of the clinically important symptoms that reflects severe or critical clinical evolution is persistent fever during the time. The presence of comorbidities, especially associated with obesity, represents a high risk of severe evolution. Proinflammatory, prothrombotic and systemic endothelial damage processes are represented by changes in platelet count, lymphocytes, neutrophil / lymphocyte ratio, C-reactive protein, D-dimers, fibrinogen, procalcitonin, urea, creatinine, ALS, AST, interleukin-6 and serum ferritin. Bacterial and fungal infections negatively influence clinical evolution. Common prediction scores have low value in COVID-19 patients and need adaptation. Imaging evaluation identifies the type of lung injury and correlates with the severity degree and outcome.
Conclusions: COVID-19 disease caused by SARS-CoV-2 virus includes a multitude of pathophysiological changes that through its mechanism represent a systemic nosology. The complete analysis of all the factors and parameters that can influence its clinical evolution is a basic component of the decision-making steps and treatment approach.
Key words: severity predictors, COVID-19, laboratory parameters, risk score, SARS-CoV-2.

Cite this article
Civirjic I, Sandru S, Arnaut O, Cernei N, Moghildea V. Factors to consider when assessing the severity of COVID-19. *Mold Med J*. 2022;65(2):51-58. https://doi.org/10.52418/moldovan-med-j.65-2.22.08.

Introduction

COVID-19 disease is an infectious pathology, transmitted by infected aerosol droplets or direct contact with surfaces contaminated by them [1], caused by the SARS-CoV-2 virus, first identified in December 2019 in Wuhan, Hubei Province, China. During the 3 months since the first identification, due to the high contagiousness, this infection had a global spread, which made in March 2020, the World Health Organization declare "Pandemic State" in connection with the increased number of cases and the global spread of this viral infection. From the beginning of the pandemic until the present, over 515400000 cases of COVID-19 infection have been confirmed with 1% of currently mortality rate [2].

COVID-19 is a polymorphic disease with the predominant clinical presentation of viral interstitial pneumonia and secondary systemic hypoxemia. But, pathophysiologically, the viral infection COVID-19, through the mechanism of viral penetration, the lesions caused at the systemic vascular level and the secondary immune response represents a systemic pathology, mirrored by the pulmonary vascular lesions. The clinical evolution is highly dependent on the secondary immune response and the detailed analysis of each stage of the disease, the predisposing factors towards an unfavourable evolution and the changes occurring in the lung and at laboratory level can guide us about disease course, the risks of adverse events and the necessity for close monitoring. During the pandemic different clinical and laboratory parameters that impact and are associated with negative outcome and mortality, but with different informativity, were highlighted. Also were applied and developed specific scores for evaluation and prognosis of clinical course.

The goal of this review is analysis and evaluation of impact and predictability of the multitude of parameters and prognostic scores that mirror clinical evolution of

COVID-19 infection. In order to realize the goal of the study was realized bibliographic search of the PubMed database, applying the keywords: "SARS-CoV-2", "COVID-19", "risk score", "laboratory parameters", "pathophysiology", "cytokine storm", "imaging evaluation", "outcomes", "clinical evolution", which were combined with each other. There were selected English-language publications, in extenso, published in recognized journals from March 2020. Priority in the analysis was given to articles of critical synthesis of literature, randomized studies, those with large samples of patients. The final bibliography included 76 references.

Discussion

1. Pathophysiology

1.1. *Cell penetration and immune reponse*

The SARS-CoV-2 virus is enveloped with a single-stranded positive sense 30 kb RNA virus, which is part of the Coronaviridae family along with the viruses HCoV-229E, HCoV-OC43, SARS-CoV, HCoV-NL63, HCoV-HKU1 and MERS-CoV [3]. The SARS-CoV-2 virus consists of 4 structural proteins: spike (S), membrane glycoprotein (M) with the role of stabilizing the viral structure, forming the envelope and releasing the viral; envelope (E) responsible for virulence and activation of the body's immunopathological response; nucleocapsid (N) that binds to viral RNA and participates in viral replication [4].

The S protein is composed of 2 subunits: S1 – responsible for binding to the host cell receptor and S2 – responsible for the fusion of viral and cell membranes. The Angiotensin-Converting Enzyme 2 receptor (ACE2) has been identified as a functional receptor for the structural protein S of SARS-COV-2 virus. The Type II transmembrane Serine Protease (TMPRSS2), which is present in the host cell, promotes viral uptake by cleavage with the ACE2 receptor and the S protein of the virus and its entry into the cell [5].

The life cycle of the virus consists of five periods: attachment, penetration, biosynthesis, maturation and release [6]. Being an RNA virus, it directly begins the production of its own protein and new genomes after penetrating the cell by attaching to ribosomes of the host cell. The ribosomes of the host cell transcribe RNA into RNA polymerase, which is then used to produce new virions in the Golgi apparatus. Newly formed virions are released from the cell by exocytosis by excretory vesicles. The release of the virus from the cell is associated with its deformation and injury. At the same time, the SARS-CoV-2 virus interferes with direct cell damage by promoting cell apoptosis [7].

The virions spread systemically, affecting the target organs that contain the high expression of ACE2 receptors and TMPRSS2 protein, which include: lungs (through type II alveolar cells), heart (through myocardial cells), arterial vascular system (through cells endothelial), kidneys (through proximal tubule cells), ileum and oesophagus (through epithelial cells), bladder (through urothelial cells) [8]. This localization of ACE2 receptors explains the clinical polymorphism of COVID-19 disease and the susceptibility or predisposition of certain population groups to the development of certain complications as well as to the evolution of the disease in severe and critical form.

The pathophysiology and clinical course of COVID-19 disease is the consequence of the T-cells mediated immune response, which produce interferon-gamma (INF-gamma) and interleukins like response to the cell invasion of the virus. Also, the damage of infected cells (especially alveolar), is the result of pro-inflammatory mediators, cytokines, interferons and other intracellular elements release. Alveolar macrophages identify cell damage and the secretion of cytokines, responding with proper secretion of cytokines and chemokines. Tumor necrosis factor (TNF), secreted by macrophages along with other proinflammatory cytokines, increases vascular permeability and cell adhesion, that induces the recruitment of other immune cells, such as neutrophils and monocytes. Neutrophils incorporate viruses and other elements from the affected area. This process is accompanied by the secretion of chemokines that leads to affect the surrounding tissues. Leukopenia associated with lymphopenia is the result of the consumption of immune cells involved in a large number in the process of immune and inflammatory response as well as the secretion of interferon [9].

1.2. *Cytokine storm*

The multitude of immune elements, cytokines and proinflammatory mediators activated by the SARS-CoV-2 invasion and cell destruction potentiate the phenomenon of "Cytokine storm", which is increasingly discussed in the context of COVID-19 disease.

Cytokine storm or Cytokine storm syndrome, is a cascade of activations and auto-amplification processes of pro-inflammatory cytokines production followed by exaggerated and dysregulated immune response of the host to various triggers (infection, rheumatic diseases, malignancies) [10].

Immune hyperactivity in cytokine storm is the result of the imbalance between the activity of pro- and anti-inflammatory processes with the predominance of proinflammatory ones. This is caused by excessive immune cell activation, pathogenic overload (e.g. sepsis), uncontrolled infections and prolonged immune activation. All this leads to the failure of the negative feedback mechanism, whose role is to control and avoid or prevent the hyperinflammatory phenomenon [11]. The clinical phenotype of the cytokine storm is largely manifested by elements of systemic inflammation, acute lung injury associated with acute respiratory distress syndrome and multiple organ dysfunction [11].

1.3. *Covid coagulopathy*

Endothelial injury caused by the virus and the immune response, which involves cytokines and leads to compliment activation, plays an important role in the association

of COVID-19 coagulopathy [12]. In this context, the involvement of neutrophils and monocytes in the "thromboinflammatory" or "immunothrombosis" process is evaluated.

The role of monocytes consists in the formation and activation of thrombo-monocyte aggregates, whose activation degree correlates with the severity of the disease and with the values of the reactive "C" protein [13].

Neutrophils are also involved in the process of micro- and macrothrombosis by forming neutrophil extracellular traps (NETs) [14]. Elevated levels of NETs closely correlate with disease severity and oxygenation disorders [15]. The presence of extracellular neutrophil traps was identified in the lungs, liver and kidneys of patients who died from COVID-19 disease [16]. Along with the mentioned immune cells, hypoxia, like a result of the multitude of proinflammatory processes in the lung capillaries, promotes thrombotic processes in patients with COVID-19 disease [17].

Hypoxia acts in 2 ways: first, the direct pathway of immunomodulin suppression and reduction of fibrinolytic potential and the second, by the formation of HIF-1a and HIF-2 transcription factors. These factors potentiate the thrombosis process by involving the inhibitor of plasminogen activation and blocking tissue factor (TF) inhibitor [18]. Therefore, in severe forms of COVID-19 disease, the hypercoagulant phenotype, with the fibrin polymerization and the resulting thrombosis, predominates over that of consumption coagulopathy [19].

The events resulting from the viral invasion on the host have a self-amplifying character, where each involved element represents a trigger and stimulates the development of a vicious pathophysiologic circle. This circle induces "cytokine storm" with prothrombotic and hypercoagulant status and the development of acute lung injury, ventilation/perfusion mismatch, pulmonary oedema, hypoxia similar to acute respiratory distress syndrome (ARDS) and promotes the development of multiple organs damage [20].

2. Severity degrees and characteristics of clinical evolution

In the clinical course of COVID-19 disease can be evident the following forms of severity [21]:

1. Asymptomatic – with positive SARS-CoV-2 test, no symptoms;

2. Mild illness – accompanied by fever, cough, anosmia and loss in taste, no dyspnea;

3. Moderate illness – with clinical or radiographic evidence of pathological changes in the lower airways and lungs, but with the maintenance of peripheral oxygen saturation (SpO2)> 94%, without oxygen support;

4. Severe illness – presence of lung infiltrates more than 50% of the total surface, SpO2 <93% without oxygen support, tachypnoea more than 30 breaths/min and signs of respiratory distress;

5. Critical illness – defined by the criteria of acute respiratory distress syndrome, sepsis, septic shock and multiple organs dysfunction.

From the total number of cases, those with asymptomatic, mild and moderate manifestations represent approximately 80% and the rest of them get severe and critical forms. The rate of Intensive Care Unit (ICU) admission of COVID-19 patients is 11% of the total number of confirmed cases [22].

There are several clinical stages in the evolution of the disease. The transition from one stage to another is not mandatory for all those infected with the SARS-CoV-2 virus.

These are:

– Incubation period – lasts on average 5.3 days;

– Early stage of disease evolution – manifested by the signs and symptoms of a seasonal viral infection (fever, myalgia, cough, fatigue, diarrhoea, anorexia) – is observed during the first 5-8 days after the symptoms onset;

– Pulmonary phase – is characterized by the appearance of dyspnea, signs of hypoxia, the appearance of opacity on lung radiography and computed tomography – develops at day 8-11 of illness;

– Hyperinflammatory phase characterized by "cytokine storm", acute respiratory distress syndrome, sepsis and septic shock – starting from day 11-15 of illness [22–25].

The factors that contribute to the progression of the disease in another phase are not fully elucidated at the moment [24]. It is assumed, that the unfavourable evolution of the disease dependents on the individual over-response of the immune system to the SARS-CoV-2 infection and on the presence of comorbidities that represent the risk factors for a severe evolution.

Management and treatment approach differs from the disease evolution stage and the patient's treatment response determins the regression of the disease or its transition to a more advanced phase [26].

In COVID-19 patients, the average time from the first symptoms onset until the admission in intensive care unit (ICU) is 9.84 days. The overall ICU mortality rate is 35.5% and the average duration from the onset of the first symptoms until death is 15.93 days [25, 27].

3. Severity predictors, evolution particularities and clinical outcome

3.1. *Demographics*

The severity of COVID-19 disease and the final outcome of survivor or non-survivor is determined by several factors and comorbidities, including: age, male gender, diabetes, chronic heart disease, cerebrovascular disease, pulmonary, renal and hepatic diseases, immunosuppression and malignancy [22]. Furthermore, obesity is one of the unfavourable predictors, and the presence of Body Mass Index (BMI) more than 30 in association with one of the factors mentioned above substantially increases the risk of disease severity [28].

The fever with values more than 38.0 and resistance to antipyretic treatment is one of the independent factors of severity and prognosis of the disease, especially in the first 5 days after the symptoms onset. Its rate is approx. 80% in symptomatic patients COVID-19 and is the common symptom in approx. 90% of patients requiring hospitalization [22, 29].

3.2. *Association of bacterial and fungal infection*

Bacterial co-infection. The pooled prevalence of bacterial co-infection identified in patients with COVID-19 disease reaches 21%. The respiratory co-infection has pooled prevalence of 5.2% and gastrointestinal 4.8% [30]. In hospitalized patients, this varies from 5.9 to 7%, with a double value of 8-14% in ICU patients. The most frequently cultivated pathogens are Mycoplasma pneumoniae (42%), Pseudomonas aeruginosa (12%) and Haemophilus influenzae (12%) [31].

Bacterial superinfection rate reaches a value of 24% in patients with COVID-19 disease, and 41% in cases of ICU patients. The most often cultivated are: Acinetobacter spp. (22.0%), Pseudomonas (10.8%), and Escherichia coli (6.9%) [32].

Ventilator Associated Pneumonia (VAP) is most common manifestation of healthcare associated bacterial superinfection in COVID-19 with rate of 50%. Bloodstream infection represents 34% of total cases and venous catheter-associated bloodstream infections – 10% [33]. The development of VAP in COVID-19 patients during mechanical ventilation serves as an aggravating factor of disease clinical course, with the mortality rate of 42.7%. These mortality values are triple higher in comparation with non-Covid-19 patients [34, 35].

Fungal infection – has a rate of 8% in COVID-19, with the predominance of Candida species (18.8%) [32].

The presence of co-infection and especially a bacterial superinfection in COVID-19 patients is an unfavourable prognostic factor, associated with an increased risk of mortality, mainly among ICU patients [31, 32].

3.3. *The laboratory predictors*

In COVID-19 clinical course can be highlighted following laboratory parameters with prognostic value of evolution, assessment of disease severity and risk or rate of adverse events (mechanical ventilation, acute kidney injury, septic shock, need in vasopressors, PE, AMI or others) [19, 36]:

- Lymphopenia – indicates severe evolution of the disease, due to increased viremia and the increased consumption of immune cells. In its case the lymphocytes number is inversely proportional to the severity of the disease [37].
- Neutrophil-lymphocyte ratio – it is a marker of stress and systemic inflammation in critically ill patients. Its value higher than 9.8 in COVID-19 patients correlates with the higher rate of ARDS and the need for non-invasive or invasive ventilatory support [38].
- Platelets count – values less than 150, are a negative prognostic factor [39]. The value less than 50 indicates very high, up to 92%, risk of death [40]. At the same time, the increase in the platelets number (which is below the normal range), during hospitalization, indicates a positive evolution and an increase in the chances of survival [41].
- Fibrinogen is a protein of acute phase which is synthesized in the liver under the interleukin-6 (IL-6) induction, like a response to a systemic inflammatory process [42]. Fibrinogen participates in the coagulation cascade and its decrease is associated with increased mortality in sepsis [43]. However, in patients with COVID-19, attention is given to high fibrinogen levels, which indicate an unfavourable outcome and a severe course of the disease [44].
- ALT / AST are liver enzymes whose values increase as a result of hepatocyte damage. In COVID-19 patients, the systemic inflammatory process or administered hepatotoxic medication can be factors that contribute to liver injury and their elevation. The amount of these enzymes guides the prognosis, and their increased values at admission are associated with an increased risk of ICU admission, the need for vasopressor support, non-invasive or mechanical ventilation and acute kidney injury [45].
- Albumin – hypoalbuminemia is a negative prognosis factor in both general groups of patients and in COVID-19 and is an independent indicator of mortality [19, 46].
- Lactate dehydrogenase (LDH) – is the enzyme that participates in the formation of energy by converting lactate to pyruvate and is present in several cells in the body. Its increase has been recorded in acute or chronic lung diseases and interstitial diseases [47]. Elevated LDH levels are an indicator of illness severity and are associated with a 6-fold higher risk of adverse outcome and respiratory worsening at values more than 450 U/l [39, 47].
- Creatinine is a marker of kidney function, which closely correlates with COVID-19 severity. Values higher than 130 mmol / l indicate a 2.6-fold increased risk of negative outcome [39]. Also, the rate of acute renal injury (AKI) in COVID-19 patients is approx. 20%, with a mortality rate of approx. 55% in case of its association [48].
- Urea values higher than 6.5 mmol/l registered at admission indicate negative evolution, poor prognosis and the greater risk of developing the severe and critical form of the illness [49].

Biomarkers

- Interleukin 6 (IL6) is a protein produced by activated monocites, macrophages and other cells. Interaction with specific receptors on responsive cells, IL-6 promotes antiviral effect, release of acute-phase reactant from hepatocytes [42]. In COVID-19, IL-6 is a reliable predictor of desease severity and ventilatory support,

where the IL- 6 levels exceeding 210 pg/mL were 100% associated with respiratory failure [50, 51]. Also, the IL-6 level recorded in ICU patient is 52% higher in comparation with non-ICU [52], and each increase in the IL-6 level of 1 pg/mL significantly increased the risk of mortality of COVID-19 patients [53].

- Serum Ferritin is a shell protein that sequesters iron in its core. Its synthesis is regulated by various "oxidant and antioxidant stimuli" and represents "acute phase reactant" that mirrors the degree of both chronic and acute inflammatory reaction inside the body [54]. A higher ferritin level indicates an activated monocyte-macrophage system, where the synthesis of ferritin is responsive to alteration in cytokine status [54]. High ferritin level is observed across a lot of inflammatory diseases and it serves as biomarker for different conditions like a rheumatologic and inflammatory disorders and cancer [54]. COVID-19 patients with severe and critical disease had higher ferritin level compared to patients with mild and moderate. Moreover, the same results were observed in non-survivors and survivors, also in ICU patients requiring mechanical ventilation and in those who didn't require ICU and did not require mechanical ventilation [54]. Additionally, higher ferritin levels correlate with presence of COVID-19 related thrombotic complications [54]. Increased ferritin value [median 1016 ng/mL (IQR 516–2534)] was reported in patients with COVID-19 related acute kidney injury compared to those without AKI [median value 680 ng/mL (IQR 315 to 1416)] [55].
- C-reactive protein (CRP) – is the inflammatory marker of the acute phase, and is produced by hepatocytes following stimulation by interleukin-6 and is used as an indicator of the severity of both inflammatory and infectious processes [56]. In the case of patients with COVID-19, it not only directly correlates with the degree and extent of pulmonary damage in the initial stage and the early pulmonary phase, but also suggests the possibility of poor prognosis and four time higher rate of negative outcome and respiratory worsening at values more than 10 mg/l [39, 47, 57, 58].

Coagulation disorders are often associated with COVID-19 infection and they are reflected by changes in coagulation tests like fibrinogen level, D-dimer, and total platelet counts. Severe forms with bad prognosis are correlated with elevated levels of D-dimers and fibrinogen and low levels of total platelet counts [44].

- D-dimers are fibrin degradation products which level indicates the increased quantity of thrombin and intense fibrinolysis process. Thromboembolic events have a high rate in patients with severe COVID-19 forms admitted in ICU. Rates of these are for venous thromboembolism – 31%, for deep vein thrombosis – 28% and for pulmonary thromboembolism – 19%, which rate is of 22% in post-mortem studies and the presence of these events is associated with 74% higher risk of mortality [59]. The high levels of D-dimers are directly proportional with the disease severity and show a 3-fold higher risk of adverse events, and the values more than 2 mcg / ml at admission predict a high risk of in-hospital mortality and are considered like an early marker of severity and therapeutic strategy. A double increase in mortality rate, from 32.8 to 52.4%, can be followed in those with D-dimer values higher than 3 mcg /ml [39, 44, 59, 60].
- Procalcitonin is a precursor of calcitonin that is normally synthesized in parafollicular C cells of the thyroid gland. In case of bacterial infection, under the action of high concentrations of TNFα and interleukins it can be synthesized by extrathyroidal tissues [61]. The synthesis of this biomarker is inhibited by interferon-(INF)-γ, which predominates in the early phase of the disease and, as a result, with the presence of normal values in non-severe evolution. The dynamical increase of this parameter levels indicates the negative evolution of the disease, the possible presence of bacterial superinfection and the 5 times increased risk of negative outcomes [62].

3.4. *Main prediction scores and their value*

In clinical practice, especially in ICU patients, different prediction scores are used for risk stratification, prognosis of clinical evolution and correction of treatment tactics.

In critical patients the most used and with a high predictive value are: APACHE II, SOFA, NEWS2, which at the beginning of the pandemic were used in COVID-19 diseases in order to stratify risks. However, it was later shown that the APACHE II score has the best predictive value in these patients, but it is significantly lower compared to non-covid patients [63]. At the same time, the use of the previously mentioned scores, which include a lot of complex parameters whose evaluation requires time, creates difficulties in the triage and analysis of patients in conditions of pandemic and overload of the medical system.

The decrease in the predictive values of nonspecific COVID-19 scores is argued by evaluating uncharacteristic for SARS-CoV-2 infection parameters of omitting others with high predictive value, such as the number of lymphocytes or D-dimers. For example, in this context, the A-DROP score, as a modification of the CURB-65, has a higher mortality predictive value than the Pneumonia Severity Index (PSI), CURB-65, CRB-65, SMART-COP, qSOFA and NEWS2 in the case of patients hospitalized with Community Acquired Pneumonia, as well as, in the case of COVID-19 patients [63,64]. Additionally, the MEWS score being one of the simplest and fastest, with a satisfactory degree of prediction [65].

The applicability of the CURB 65, NEWS-2 and qSOFA scores remains debatable in the context of the moderate prognostic level and underestimation of the mortality rate in patients with COVID-19 disease [66].

3.5. *COVID-19 prediction scores*

During the pandemic, many factors associated with the increased mortality were identified and were adapted several prediction models. The common parameters that were included in most of them are: lymphocytes number, D-dimers, CRP, platelet count, neutrophil-lymphocyte ratio, LDH, oxygen saturation and the presence of comorbidities. For example, Covichem score which includes 2 clinical and 5 biochemical parameters [67], COVID-19 Scoring System (CSS) which evaluates 4 parameters (procalcitonin, D-dimers, lymphocytes (%) and the presence of cardiovascular pathology) [68], ABC2-SPH mortality risk score that analyses 7 parameters (age, SpO2 / FiO2 ratio, platelet count, CRP values) [69].

In the list of the developed and validated for COVID-19 scores is also included the ISARIC score, which was evaluated in 75000 patients and was validated and applied in 9 regions of the United Kingdom [70]. This score evaluates 11 parameters at hospital admission or at first contact with a patient. This is the number of comorbidities, age, sex, presence of pulmonary infiltrates, urea level, respiratory rate, CRP, lymphocyte number, oxygen saturation. After introducing the required parameters depending on the score obtained, is stratified and assessed the risk of two evolutions – deterioration and mortality. The calculated risks are presented in percentage values. Unfortunately, the value of D-dimers was not included in the prediction parameters of this score, because it was present and analysed in a small number of participants included in the study [70].

3.6. *Scores for imaging evaluation and standardization*

Imaging assessment of the lung lesions severity plays an important role in the analysis and stratification of the COVID-19 evolution.

The gold standard in the imaging evaluation of the degree and type of lung modification, as well as of the evolutionary stage, is represented by Computed Tomography (CT-scan). The main changes that can be identified on CT are: vascular enlargement (84.8%), followed by ground-glass opacity (60.1%), air-bronchogram (47.8%) and lung consolidations (41.4%) [71]. Likewise, it can establish the location of the changes and the degree and extent of the spread. The CO-RADS score and the CT Severity Score (CSS) are used to standardize the severity of the lung damage. The CO-RADS score accuracy in estimating is slightly higher and both of them, closely correlate with the disease severity and changes in laboratory parameters with prediction of negative evolution [72, 73].

The overload of the medical system and the large flow of patients create impediments in imaging evaluation by computed tomography. Dynamical examination of lung infiltrates evolution requires transporting to the CT scan that is associated with certain risks, especially in severe or critically ill connected to non-invasive or mechanical ventilation. Like an alternative, the role in imaging evaluation in this situation was taken by the chest X-ray, which has a lower diagnostic value compared to computed tomography, but can be easier, faster and dynamically performed in ICU patient.

In March 2020, a group of Italian authors, based on radiological images of patients with COVID-19, developed a new system for grading the severity of lung damage, specific to the type and form of tissue damage encountered in SARS-CoV-2 infection, called Brixia Score [74]. Subsequent research has shown a close correlation of the Brixia Score with both the severity of the disease and the prognosis [75, 76]. This score includes two stages of analysis of the radiological image. In the first step, the lungs are divided into six zones on frontal chest projection (posteroanterior or anteroposterior projection according to the patient position). In the second step, a score (from 0 to 3) is assigned to each zone based on the lung abnormalities detected on frontal chest projection as follows [74]:

- *Score 0* no lung abnormalities,
- *Score 1* interstitial infiltrates,
- *Score 2* interstitial and alveolar infiltrates (interstitial predominance),
- *Score 3* interstitial and alveolar infiltrates (alveolar predominance).

The scores of the six lung zones are then added to obtain an overall "CXR SCORE" ranging from 0 to 18.

The application of this score standardized the analysis and calculation of the degree of lung damage in COVID-19 patients by radiologists giving it diagnostic severity and prognostic value [75].

Conclusions

COVID-19 disease caused by SARS-COV-2 virus includes a multitude of pathophysiological changes that through its mechanism represent a systemic nosology. The complete analysis of all the factors and parameters that can influence its clinical evolution, especially in patients at risk groups, is a basic component of the decision-making steps, management tactics and treatment approach.

References

1. European Centre for Disease Prevention and Control. Transmission of COVID-19 [Internet]. Stockholm: ECDC; 2022- [cited 2022 May 5]. Available from: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/transmission
2. Worldometers.info. COVID Live - Coronavirus Statistics [Internet]. Dover, USA; 2022- [cited 2022 May 5]. Available from: https://www.worldometers.info/coronavirus/
3. Rabi FA, Al Zoubi MS, Al-Nasser AD, Kasasbeh GA, Salameh DM. SARS-CoV-2 and Coronavirus Disease 2019: what we know so far. Pathogens. 2020;9(3):231. doi: 10.3390/PATHOGENS9030231.
4. Satarker S, Nampoothiri M. Structural proteins in Severe Acute Respiratory Syndrome Coronavirus-2. Arch Med Res. 2020;51(6):482. doi: 10.1016/J.ARCMED.2020.05.012.
5. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-280.e8. doi:10.1016/J.CELL.2020.02.052.
6. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol. 2020;215:108427. doi: 10.1016/J.CLIM.2020.108427.

7. Astuti I, Ysrafil. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): an overview of viral structure and host response. Diabetes Metab Syndr Clin Res Rev. 2020;14(4):407-412. doi: 10.1016/J.DSX.2020.04.020.
8. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. 2020;14(2):185-192. doi: 10.1007/S11684-020-0754-0.
9. Rahman S, Montero MTV, Rowe K, Kirton R, Kunik F. Epidemiology, pathogenesis, clinical presentations, diagnosis and treatment of COVID-19: a review of current evidence. Expert Rev Clin Pharmacol. 2021;14(5):1. doi: 10.1080/17512433.2021.1902303.
10. Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in COVID-19: the current evidence and treatment strategies. Front Immunol. 2020;11:1708. doi: 10.3389/FIMMU.2020.01708/FULL.
11. Fajgenbaum DC, June CH. Cytokine storm. N Engl J Med. 2020;383(23):2255-2273. doi: 10.1056/NEJMra2026131.
12. Goswami J, MacArthur TA, Sridharan M, et al. A review of pathophysiology, clinical features, and management options of COVID-19 associated coagulopathy. Shock. 2021;55(6):700. doi: 10.1097/SHK.0000000000001680.
13. Hottz ED, Azevedo-Quintanilha IG, Palhinha L, et al. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. Blood. 2020;136(11):1330. doi: 10.1182/BLOOD.2020007252.
14. Fuchs TA, Brill A, Wagner DD. Neutrophil extracellular trap (NET) impact on deep vein thrombosis. Arterioscler Thromb Vasc Biol. 2012;32(8):1777-1783. doi: 10.1161/ATVBAHA.111.242859.
15. Zuo Y, Yalavarthi S, Shi H, et al. Neutrophil extracellular traps in COVID-19. JCI Insight. 2020;5(11). doi: 10.1172/JCI.INSIGHT.138999.
16. Middleton EA, He XY, Denorme F, et al. Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome. Blood. 2020;136(10):1169-1179. doi: 10.1182/BLOOD.2020007008.
17. Thachil J. Hypoxia – an overlooked trigger for thrombosis in COVID-19 and other critically ill patients. J Thromb Haemost. 2020;18(11):3109-3110. doi: 10.1111/JTH.15029.
18. Gupta N, Zhao YY, Evans CE. The stimulation of thrombosis by hypoxia. Thromb Res. 2019;181:77-83. doi: 10.1016/J.THROMRES.2019.07.013.
19. Gallo Marin B, Aghagoli G, Lavine K, et al. Predictors of COVID-19 severity: a literature review. Rev Med Virol. 2021;31(1):1-10. doi: 10.1002/RMV.2146.
20. Liu J, Zheng X, Tong Q, et al. Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. J Med Virol. 2020;92(5):491-494. doi: 10.1002/JMV.25709.
21. World Health Organization. Living guidance for clinical management of COVID-19. Geneva: WHO; 2021 [cited 2022 May 5]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2
22. Li J, Huang DQ, Zou B, et al. Epidemiology of COVID-19: a systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes. J Med Virol. 2021;93(3):1449-1458. doi: 10.1002/JMV.26424.
23. Xie Y, Wang Z, Liao H, Marley G, Wu D, Tang W. Epidemiologic, clinical, and laboratory findings of the COVID-19 in the current pandemic: systematic review and meta-analysis. BMC Infect Dis. 2020;20(1):1-12. doi: 10.1186/S12879-020-05371-2/FIGURES/3.
24. dos Santos WG. Natural history of COVID-19 and current knowledge on treatment therapeutic options. Biomed Pharmacother. 2020;129:110493. doi: 10.1016/J.BIOPHA.2020.110493.
25. Khalili M, Karamouzian M, Nasiri N, Javadi S, Mirzazadeh A, Sharifi H. Epidemiological characteristics of COVID-19: a systematic review and meta-analysis. Epidemiol Infect. 2020;148. doi: 10.1017/S0950268820001430.
26. Gandhi RT. The multidimensional challenge of treating coronavirus disease 2019 (COVID-19): remdesivir is a foot in the door. Clin Infect Dis. 2021;73(11):e4175-e4178. doi: 10.1093/CID/CIAA1132.
27. Armstrong RA, Kane AD, Kursumovic E, Oglesby FC, Cook TM. Mortality in patients admitted to intensive care with COVID-19: an updated systematic review and meta-analysis of observational studies. Anaesthesia. 2021;76(4):537-548. doi: 10.1111/ANAE.15425.
28. Hernández-Garduño E. Obesity is the comorbidity more strongly associated for Covid-19 in Mexico. A case-control study. Obes Res Clin Pract. 2020;14(4):375-379. doi: 10.1016/J.ORCP.2020.06.001.
29. Chew NW, Ngiam JN, Tham SM, et al. Fever as a predictor of adverse outcomes in COVID-19. QJM An Int J Med. 2021;114(10):706-714. doi: 10.1093/QJMED/HCAB023.
30. Soltani S, Faramarzi S, Zandi M, et al. Bacterial coinfection among coronavirus disease 2019 patient groups: an updated systematic review and meta-analysis. New Microbes New Infect. 2021;43:100910. doi: 10.1016/J.NMNI.2021.100910.
31. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect. 2020;81(2):266-275. doi: 10.1016/J.JINF.2020.05.046.
32. Musuuza JS, Watson L, Parmasad V, Putman-Buehler N, Christensen L, Safdar N. Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: a systematic review and meta-analysis. PLoS One. 2021;16(5):e0251170. doi: 10.1371/JOURNAL.PONE.0251170.
33. da Silva Ramos FJ, de Freitas FGR, Machado FR. Sepsis in patients hospitalized with coronavirus disease 2019: how often and how severe? Curr Opin Crit Care. 2021;27(5):474-479. doi: 10.1097/MCC.0000000000000861.
34. Ippolito M, Misseri G, Catalisano G, et al. Ventilator-associated pneumonia in patients with covid-19: a systematic review and meta-analysis. Antibiotics. 2021;10(5):545. doi: 10.3390/ANTIBIOTICS10050545/S1.
35. Maes M, Higginson E, Pereira-Dias J, et al. Ventilator-associated pneumonia in critically ill patients with COVID-19. Crit Care. 2021;25(1):1-11. doi: 10.1186/S13054-021-03460-5/FIGURES/4.
36. Ou M, Zhu J, Ji P, et al. Risk factors of severe cases with COVID-19: a meta-analysis. Epidemiol Infect. 2020;148. doi: 10.1017/S095026882000179X.
37. Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther. 2020;5(1):1-3. doi: 10.1038/s41392-020-0148-4.
38. Ma A, Cheng J, Yang J, Dong M, Liao X, Kang Y. Neutrophil-to-lymphocyte ratio as a predictive biomarker for moderate-severe ARDS in severe COVID-19 patients. Crit Care. 2020;24(1):288. doi: 10.1186/S13054-020-03007-0.
39. Malik P, Patel U, Mehta D, et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. BMJ Evidence-Based Med. 2021;26(3):107-108. doi: 10.1136/BMJEBM-2020-111536.
40. Yang X, Yang Q, Wang Y, et al. Thrombocytopenia and its association with mortality in patients with COVID-19. J Thromb Haemost. 2020;18(6):1469-1472. doi: 10.1111/JTH.14848.
41. Chen R, Sang L, Jiang M, et al. Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. J Allergy Clin Immunol. 2020;146(1):89-100. doi: 10.1016/J.JACI.2020.05.003.
42. Kerr R, Stirling D, Ludlam CA. Interleukin 6 and haemostasis. Br J Haematol. 2001;115(1):3-12. doi: 10.1046/J.1365-2141.2001.03061.X.
43. Matsubara T, Yamakawa K, Umemura Y, et al. Significance of plasma fibrinogen level and antithrombin activity in sepsis: a multicenter cohort study using a cubic spline model. Thromb Res. 2019;181:17-23. doi: 10.1016/J.THROMRES.2019.07.002.
44. Lin J, Yan H, Chen H, et al. COVID-19 and coagulation dysfunction in adults: a systematic review and meta-analysis. J Med Virol. 2021;93(2):934-944. doi: 10.1002/JMV.26346.
45. Piano S, Dalbeni A, Vettore E, et al. Abnormal liver function tests predict transfer to intensive care unit and death in COVID-19. Liver Int. 2020;40(10):2394-2406. doi: 10.1111/LIV.14565.
46. Huang J, Cheng A, Kumar R, et al. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. J Med Virol. 2020;92(10):2152-2158. doi: 10.1002/JMV.26003.
47. Poggiali E, Zaino D, Immovilli P, et al. Lactate dehydrogenase and C-reactive protein as predictors of respiratory failure in CoVID-19 patients. Clin Chim Acta. 2020;509:135-138. doi: 10.1016/J.CCA.2020.06.012.
48. Raina R, Mahajan ZA, Vasistha P, et al. Incidence and outcomes of acute kidney injury in COVID-19: a systematic review. Blood Purif. 2022;51(3):199-212. doi: 10.1159/000514940.
49. Hachim MY, Hachim IY, Naeem K Bin, Hannawi H, Salmi I Al, Hannawi S. D-dimer, troponin, and urea level at presentation with

COVID-19 can predict ICU admission: a single centered study. Front Med. 2020;7:949. doi: 10.3389/FMED.2020.585003/BIBTEX.
50. Liu X, Wang H, Shi S, Xiao J. Association between IL-6 and severe disease and mortality in COVID-19 disease: a systematic review and meta-analysis. Postgrad Med J. 2021;98(1165):871-879. doi: 10.1136/POSTGRADMEDJ-2021-139939.
51. Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol. 2020;146(1):128-136.e4. doi: 10.1016/J.JACI.2020.05.008.
52. Prompetchara E, Ketloy C, Palaga T. Allergy and Immunology Immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol. 2020;38(1):1-9. doi: 10.12932/AP-200220-0772.
53. Halim C, Mirza AF, Sari MI. The association between TNF-α, IL-6, and Vitamin D levels and COVID-19 severity and mortality: a systematic review and meta-analysis. Pathogens. 2022;11(2):195. doi: 10.3390/pathogens11020195.
54. Kaushal K, Kaur H, Sarma P, et al. Serum ferritin as a predictive biomarker in COVID-19. A systematic review, meta-analysis and meta-regression analysis. J Crit Care. 2022;67:172-181. doi: 10.1016/J.JCRC.2021.09.023.
55. Mohamed MMB, Lukitsch I, Torres-Ortiz AE, et al. Acute kidney injury associated with Coronavirus Disease 2019 in urban New Orleans. Kidney360. 2020;1(7):614. doi: 10.34067/KID.0002652020.
56. Wang L. C-reactive protein levels in the early stage of COVID-19. Médecine Mal Infect. 2020;50(4):332-334. doi: 10.1016/J.MEDMAL.2020.03.007.
57. Tan C, Huang Y, Shi F, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol. 2020;92(7):856-862. doi: 10.1002/JMV.25871.
58. Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: a systematic review and meta-analysis. EClinicalMedicine. 2020;29-30:100639. doi: 10.1016/J.ECLINM.2020.100639.
59. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. J Thromb Thrombolysis. 2021;51(4):1107. doi: 10.1007/S11239-020-02105-8.
60. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020;18(6):1324-1329. doi: 10.1111/JTH.14859.
61. Lippi G, Cervellin G. Procalcitonin for diagnosing and monitoring bacterial infections: for or against? Clin Chem Lab Med. 2018;56(8):1193-1195. doi: 10.1515/CCLM-2018-0312/PDF.
62. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chim Acta. 2020;505:190. doi: 10.1016/J.CCA.2020.03.004.
63. Chu K, Alharahsheh B, Garg N, Guha P. Evaluating risk stratification scoring systems to predict mortality in patients with COVID-19. BMJ Health Care Informatics. 2021;28(1):100389. doi: 10.1136/BMJHCI-2021-100389.
64. Fan G, Tu C, Zhou F, et al. Comparison of severity scores for COVID-19 patients with pneumonia: a retrospective study. Eur Respir J. 2020;56(3). doi: 10.1183/13993003.02113-2020.
65. Wang L, Lv Q, Zhang X, et al. The utility of MEWS for predicting the mortality in the elderly adults with COVID-19: a retrospective cohort study with comparison to other predictive clinical scores. PeerJ. 2020;8:e10018. doi: 10.7717/PEERJ.10018/SUPP-5.
66. Bradley P, Frost F, Tharmaratnam K, Wootton DG. Utility of established prognostic scores in COVID-19 hospital admissions: multicentre prospective evaluation of CURB-65, NEWS2 and qSOFA. BMJ Open Respir Res. 2020;7(1):e000729. doi: 10.1136/BMJRESP-2020-000729.
67. Bats ML, Rucheton B, Fleur T, et al. Covichem: a biochemical severity risk score of COVID-19 upon hospital admission. PLoS One. 2021;16(5):e0250956. doi: 10.1371/JOURNAL.PONE.0250956.
68. Shang Y, Liu T, Wei Y, et al. Scoring systems for predicting mortality for severe patients with COVID-19. EClinicalMedicine. 2020;24:100426. doi: 10.1016/J.ECLINM.2020.100426.
69. Marcolino MS, Pires MC, Ramos LEF, et al. ABC2-SPH risk score for in-hospital mortality in COVID-19 patients: development, external validation and comparison with other available scores. Int J Infect Dis. 2021;110:281-308. doi: 10.1016/J.IJID.2021.07.049.
70. Gupta RK, Harrison EM, Ho A, et al. Development and validation of the ISARIC 4C. Deterioration model for adults hospitalised with COVID-19: a prospective cohort study. Lancet Respir Med. 2021;9(4):349-359. doi: 10.1016/S2213-2600(20)30559-2.
71. Ghayda RA, Lee KH, Kim JS, et al. Chest CT abnormalities in covid-19: a systematic review. Int J Med Sci. 2021;18(15):3395-3402. doi: 10.7150/IJMS.50568.
72. Zayed NE, Bessar MA, Lutfy S. CO-RADS versus CT-SS scores in predicting severe COVID-19 patients: retrospective comparative study. Egypt J Bronchol. 2021;15(1):1-10. doi: 10.1186/S43168-021-00060-3.
73. Canovi S, Besutti G, Bonelli E, et al. The association between clinical laboratory data and chest CT findings explains disease severity in a large Italian cohort of COVID-19 patients. BMC Infect Dis. 2021;21(1):1-9. doi: 10.1186/S12879-021-05855-9.
74. Borghesi A, Maroldi R. COVID-19 outbreak in Italy: experimental chest X-ray scoring system for quantifying and monitoring disease progression. Radiol Medica. 2020;125(5):509-513. doi: 10.1007/S11547-020-01200-3.
75. Maroldi R, Rondi P, Agazzi GM, Ravanelli M, Borghesi A, Farina D. Which is the role for chest X-ray score in predicting the outcome in COVID-19 pneumonia? Eur Radiol. 2021;31(6):4016-4022. doi: 10.1007/S00330-020-07504-2.
76. Borghesi A, Zigliani A, Golemi S, et al. Chest X-ray severity index as a predictor of in-hospital mortality in coronavirus disease 2019: a study of 302 patients from Italy. Int J Infect Dis. 2020;96:291-293. doi: 10.1016/J.IJID.2020.05.021.

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Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics approval and consent to participate. No approval was required for this study.

Conflict of interests . The authors have no conflict of interests to declare.