Mini Review

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Biochemical biomarkers alterations in Coronavirus Disease 2019 (COVID-19)

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Abstract: Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a respiratory disease, which can evolve into multi-organ failure (MOF), leading to death. Several biochemical alterations have been described in COVID-19 patients. To date, many biomarkers reflecting the main pathophysiological characteristics of the disease have been identified and associated with the risk of developing severe disease. Lymphopenia represents the hallmark of the disease, and it can be detected since the early stage of infection. Increased levels of several inflammatory biomarkers, including c-reactive protein, have been found in COVID-19 patients and associated with an increased risk of severe disease, which is characterised by the so-called "cytokine storm". Also, the increase of cardiac and liver dysfunction biomarkers has been associated with poor outcome. In this review, we provide an overview of the main biochemical characteristics of COVID-19 and the associated biomarkers alterations.

Keywords: biochemical alterations; biomarkers; COVID-19; laboratory; SARS-CoV-2.

Introduction

The severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), which belongs to the Coronaviridae family, causes a highly transmittable acute respiratory disease, defined by the World Health Organization (WHO) as Coronavirus Disease 2019 (COVID-19). The first cases of COVID-19 were detected in Wuhan, Hubei Province, People's Republic of China, at the end of 2019. Since then, the illness spread rapidly around the country and the world reaching a pandemic level [1]. On 30 January 2020, the WHO declared the outbreak of COVID-19 to be a "public health emergency of international concern".

The Coronaviridae family consists of enveloped, single positive-strand RNA viruses classified in four sub-groups: α-coronavirus (α-COV), β-coronavirus (β-COV), δ-coronavirus (δ-COV) and γ-coronavirus (γ-COV) [2]; SARS-CoV-2 is a β-COV. Among β-COV, SARS-CoV and the Middle East Respiratory Syndrome CoronaVirus (MERS-CoV) are highly pathogenic viruses, which represented a public concern over the past two decades causing lethal human illness. The SARS-CoV (now named SARS-CoV-1) was discovered in November 2002 in Guangdong, China, and subsequently spread rapidly worldwide to 29 countries [3]. Only a decade later (June 2012), MERS-CoV caused an endemic in Middle Eastern countries [4].

Coronaviruses can infect animals and/or humans, with some strains being zoonotic. The SARS-CoV outbreak in 2002 originated from bats in China [5] and the MERS-CoV outbreak in 2012 from dromedary camels, though also likely transmitted from bats, in the Middle East [6]. It has been hypothesised that SARS-CoV-2 might be transmitted by bats [7], snakes [8], or pangolins [9]. It is a virus highly transmissible from human to human through respiratory droplets and aerosols. The incubation period of COVID-19 could vary from 1 to 14 days and results in respiratory tract infection characterized by a broad spectrum of clinical manifestations with a different degree of severity, from asymptomatic patients to pneumonia evolving into acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF), leading to death [10]. Elderly (>65 years) and individuals with associated comorbidities, such as diabetes, hypertension, and chronic obstructive pulmonary disease, are more susceptible to severe disease.

The laboratory provides critical support for the appropriate clinical management of COVID-19, from screening to diagnosis, prognosis, and monitoring [11]. In this review, we provide an overview of the biochemical alterations associated with COVID-19.

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Biochemical profiles alterations

According to the severity of the disease, the clinical course of COVID-19 can be classified into three stages, namely "early infection", "pulmonary phase", and "hyperinflam mation phase", each one characterised by specific biochemical alterations [12] (Figure 1).

The first stage occurs at the time of the infiltration of the virus in the lung parenchyma, where SARS-CoV-2 infects ciliated bronchial epithelial cells through the interaction with the angiotensin-converting enzyme 2 (ACE2). ACE2 is a monocarboxypeptidase with a critical role in regulating the cleavage of several peptides within the renin-angiotensin system. It is highly expressed on pneumocytes in the lung [13]. At this stage, most of the patients present non-specific symptoms, such as dry cough and fever, associated with an initial inflammatory response due to the innate immunity, mainly monocytes and macrophages [14]. Lymphocytopenia is a hallmark of this stage.

The pulmonary phase is characterised by established pulmonary disease (viral pneumonia), associated with localised inflammation within the lung. Biochemical characteristics include lymphopenia and an increase of transaminases as well as systemic inflammation biomarkers, such as C-reactive protein (CRP). At this stage, most of the patients require hospitalization.

The third stage of COVID-19 is the most severe, characterised by systemic inflammation, or cytokine storm, leading to ARDS and MOF [15]. At this stage, patients should be admitted to an Intensive Care Unit (ICU). Several inflammatory biomarkers are significantly increased. Moreover, most of the patients present cardiac and kidney injury, which can be detected by circulating biomarkers. Also, alterations of the central nervous system (CNS) have been described [16]. Figure 2 and Table 1 summarise the main biochemical alterations found in COVID-19 patients.

Haematological alterations

Lymphopenia represents the most common laboratory finding detected at the cell blood count (CBC) in COVID-19

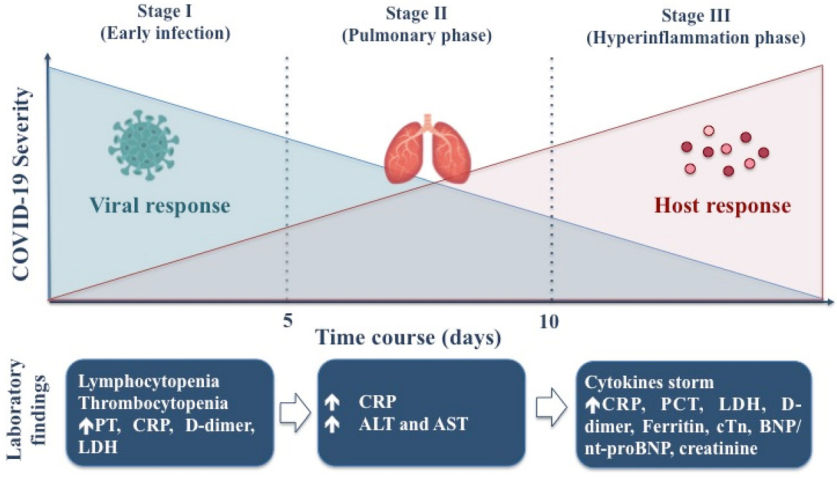

Figure 1: Disease progression and main laboratory findings.

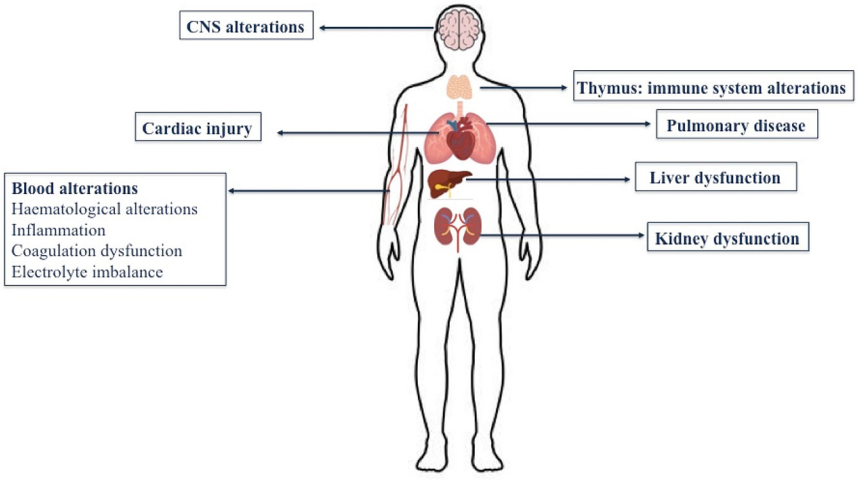

Figure 2: Main biochemical alterations associated with COVID-19.

Table 1: Main biochemical alterations in severe COVID-19 patients.

Alteration	Biomarkers
Haematological	↓ Lymphocyte count
	↑ Neutrophil count
	↑ NLR
	↓ Platelet count
Inflammatory	↑ ERS
	↑ CRP
	↑ PCT
	↑ Ferritin
	↑ IL-6
	↑ LDH
	↑ MDW
Coagulation	↑ D-dimer
	↑ FDP
	↑ PT
	↑ aPTT
	↑ Fibrinogen
Electrolyte	↓ K^+
	↓ Na^+
	↓ Ca^{++}
Hepatic	↑Alanine aminotransferase
	↑ Aspartate aminotransferase
	↑ Total bilirubin
	↓ Albumin
Muscular	↑ CK
	↑ Mioglobin
Renal	↑ Creatinine
Cardiac	↑ cTn
	↑ BNP/nt-proBNP

ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotrasnferase; BNP, brain natriuretic peptide; CK, creatine kinase; CNS, central nervous system; cTn, cardiac Troponin; CRP, c-reactive protein; FDP, fibrin degradation products; LDH, dactate dehydrogenase; NLR, neutrophils-to-lymphocytes ratio; PCT, procalcitonin; PT, prothrombin time.

patients, since the initial stage of early infection. Several mechanisms have been proposed to explain the reduced lymphocyte levels. As showed for SARS-CoV, it has been hypothesized that the virus might directly infect lymphocytes, principally T cells, inducing depletion of $CD4^+$ and $CD8^+$ cells [17, 18, 19] and, thus, suppressing the cellular immune response [13, 20, 21]. The evidence that lymphocytes express the ACE2 receptor on their cellular membrane supports such a hypothesis [10]. Additionally, the virus might directly destroy lymphatic organs. However, this hypothesis needs to be confirmed by the evidence of pathological dissection in such organs. Finally, pro-inflammatory cytokines, such as IL-6 and TNF-alpha, could induce lymphocyte deficiency [22].

Leucocytosis, especially neutrophilia, is another SARS-CoV2 infection-induced alteration detectable at the CBC of COVID-19 patients [23–26]. Some authors proposed neutrophil-to-lymphocyte ratio (NLR) as an independent risk factor for severe disease [27, 28]. Elevated NLR, resulting from the increased neutrophil count and decreased lymphocyte count, has been reported to be significantly associated with an increased risk of all-cause death during hospitalization of COVID-19 patients.

Finally, thrombocytopenia has been described in COVID-19 patients and associated with the progression and prognosis of the disease [29]. Several causes can induce platelet deficiency, such as the direct SARS-CoV2 infection of haematopoietic cells or bone marrow stromal cells, leading to haematopoietic inhibition [30]. The lung injury could also contribute to the platelet depletion due to the activation, aggregation, and retention of platelets in the lung, and the formation of thrombus at the injured site, leading to decreased platelet production and increased consumption [31, 32].

Inflammation

The hallmark of severe COVID-19 is the hyperinflammatory host response due to the so-called “cytokine storm”, defined as an uncontrolled systemic inflammatory response due to the release of large amounts of pro-inflammatory cytokines, resulting from the SARS-CoV-2 induced activation of both natural and cellular immunity.

Increased levels of several inflammatory biomarkers, including cytokines such as IL-6, IL-2, IL-7, TNF-α, interferon (IFN)-γ, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1α, granulocyte-colony stimulating factor (G-CSF), and CRP, procalcitonin (PCT), lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR) and ferritin, have been reported in COVID-19 patients. Among inflammatory biomarkers, CRP levels increase significantly at the early stage of the disease, and a positive correlation between increased CRP levels and disease severity has been described [13, 20, 33, 34]. Tan et al. [35] showed that CRP has good diagnostic accuracy in early predicting severe COVID-19 at a cut-off value of 20.42 mg/L (area under the curve [AUC] 0.87, 95% Confidence Interval [CI] 0.10–1.00, sensitivity and specificity 83% and 91%). Overall, literature evidence suggests that in the early stage of COVID-19, CRP levels could reflect disease severity.

Circulating PCT levels are commonly within the normal range in COVID-19 patients, as expected for a viral infection. However, increased levels have been associated with a 5-fold higher risk of evolution towards severe disease [36]. The significant increase of PCT could reflect a

bacterial co-infection. However, such a hypothesis must be confirmed.

A new promising biomarker of infection and sepsis is the monocyte distribution width (MDW), a measure of the dispersion around the mean of the monocyte volume population in whole blood. Two studies [26, 37], as well as our analysis (personal data, not shown), revealed increased MDW levels in severe COVID-19 patients.

Finally, elevated levels of the anti-inflammatory interleukin-10 (IL-10) have also been reported in severe COVID-19 patients. This may be due to the compensatory anti-inflammatory response, which could partially explain the high risk of secondary infections and sepsis reported in non-survivors [38].

Coagulation dysfunction

A hypercoagulable state, which might promote thrombotic coagulopathies such as pulmonary microthrombosis and disseminated intravascular coagulation (DIC), is a common complication of severe COVID-19 [18–20, 39, 40].

The underlying pathological mechanisms include infection-related dysfunction of endothelial cells, which causes an increased production of thrombin and inhibition of the fibrinolysis; cardiovascular injury; hyperinflammation state; prolonged immobilisation due to the illness; mechanical ventilation; and central venous catheters [41–43]. Additionally, the hypoxemia associated with severe pneumonia can promote thrombosis by increasing blood viscosity and activating signalling pathway. Liver dysfunction could also impair the production of coagulation factors [43]. Finally, underlying traditional risk factors, such as genetic background (FV Leiden and FIIG20210A), perinuclear anti-neutrophil cytoplasmic antibodies (pANCA), and previous history of venous thromboembolism (VTE), may significantly contribute to an increased risk of thrombotic events in COVID-19 patients [43, 44].

Increased D-dimer levels found in severe COVID-19 patients reflect the coagulation alterations [20, 21, 45]. Noteworthy, D-dimer levels are associated with a poor outcome defined as an increased risk of ARDS, ICU admission, and mortality [19, 38, 46]. Also increased fibrinogen, fibrin degradation products (FDP) levels, prothrombin time (PT) and activated partial thromboplastin time (aPTT) during the early phase of COVID-19 have been associated with severe disease [45].

Due to the high risk of DIC and VTE, hospitalised COVID-19 patients should receive thromboprophylaxis, as suggested by guidelines for the clinical management of acute illness patients [47, 48]. However, data on the potential beneficial effect of anticoagulant therapy in COVID-19 are very limited. Thus, further studies are warranted to support its use and to define therapeutic indications.

Electrolyte imbalance

Some authors described alterations of electrolyte levels, including sodium, potassium, chloride, and calcium, in COVID-19 patients [17, 19]. Specifically, hyponatremia, hypokalemia, and hypocalcemia have been associated with severe disease [49]. Although pathophysiological mechanisms underlying such alterations are not fully understood yet, some hypotheses have emerged. The interaction of SARS-Cov-2 with ACE2 receptor might reduce ACE2 expression, resulting in an increased angiotensin II, which promote potassium excretion, leading to hypokalemia [50]. Also, gastrointestinal impairment, characterised by diarrhoea, could contribute to electrolyte disequilibrium [51].

To date, only a few studies evaluated the electrolyte status upon patient presentation. Thus, further prospective cohort studies are needed in order to define its clinical implication [49].

Liver dysfunction

The alteration of hepatocytes damage biomarkers, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and albumin, is a common laboratory finding in COVID-19 patients. However, the underlying mechanism is not fully understood. Although hepatocytes and bile duct epithelial cells express ACE2 receptor [52], no significant altered histopathological features have been detected in such cells from COVID-19 patients [15]. Thus, COVID-19-related liver dysfunction could be the result of secondary liver damage due to the administration of hepatotoxic drugs, systemic inflammatory response, respiratory distress syndrome-induced hypoxia, and MOF [53].

Increased levels of liver dysfunction biomarkers have been associated with severe COVID-19 and a worse prognosis [26].

Muscle injury

COVID-19 patients typically present increased levels of biomarkers of muscle injury, namely creatine-kinase (CK) and myoglobin [26]. However, the alterations of such biomarkers

could be the result of several clinical conditions, including kidney dysfunction and cardiac injury, or a direct effect of the SARS-CoV-2, which can also infect cells of the muscle tissue due to the expression of the ACE2 receptor.

Kidney dysfunction

Several studies reported kidneys alterations, as reflected by increased serum creatinine, in COVID-19 patients. SARS-CoV-2 could directly infect kidney tubular cells, which express the ACE2 receptor on their cellular surface. Moreover, circulating mediators could interact with kidney-resident cells resulting in endothelial dysfunction, microcirculatory derangement, and tubular injury [54].

About 25–30% of COVID-19 patients develop acute kidney injury (AKI) as reported by the Italian Report of "Istituto Superiore di Sanità" (https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-201917marzo-v2.pdf). AKI has been associated with increased mortality risk [55].

Cardiac injury

A common characteristic of COVID-19 patients is cardiac injury, which could result from direct and indirect effects of the SARS-CoV2 infection on cardiomyocytes, including acute myocardial infarction (IMA), heart failure, impaired renal function (leading to troponin accumulation), myocarditis, arrhythmias, cardiac arrest, sepsis, septic shock, and pulmonary embolism (PE) [56]. Although the underlying mechanisms have not been fully established, some hypothesis has emerged, including cardiac stress due to respiratory failure and hypoxemia; direct SARS-CoV2 infection of myocardial cells which express ACE2 receptor; and indirect alterations due to systemic inflammatory response [14].

The increase of cardiac troponin (cTn) and brain natriuretic peptide (BNP)/NT-proBNP has been associated with worse prognosis [20, 38, 56–59]. Thus, the evaluation of cardiac damage biomarkers upon admission in hospital and the longitudinal monitoring during hospital stay could represent an important tool for the early detection of cardiac injury, allowing prompt intervention, in order to improve the clinical outcome of COVID-19 patients [56].

Conclusions

Laboratory medicine has a crucial role for the appropriate COVID-19 management since the early recognition to the assessment of disease severity and the prediction risk of evolution towards severe disease, characterised by the impairment of several organs and tissues. The latter can be due to both indirect and direct effects of SARS-CoV-2 infection. Indeed, the virus can infect cells through the interaction with the ACE2 receptor, which is highly expressed in many organs and tissues.

The SARS-CoV-2 infection results in a respiratory disease characterised by several biochemical alterations, which can be detected by specific biomarkers, allowing clinicians to ensure adequate clinical monitoring, the institution of supportive interventions, and improving the clinical outcome [60, 61].

Many biomarkers have been associated with poor outcomes and represent a candidate for risk stratification models for predicting severe COVID-19 in order to guide clinical care. Among all, lymphopenia, thrombocytopenia, leucocytosis, CRP, PCT, LDH, AST, ALT, D-dimer, cTn represent the most predictive parameters of severe COVID-19 [17, 26]. In addition to traditional biochemical biomarkers, it would be interesting to assess the role of new promising biomarkers, such as presepsin and MDW, for the early identification of patients at increased risk of complications [62, 63].

Finally, another interesting field of research is the study of the immunological alterations as reflected by serum tests, such as immunoglobulin A (IgA), IgM, and IgG, in order to fully understand the response of the immune system to the SARS-CoV-2 infection [64, 65].

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