REVIEW ARTICLE

Laboratory findings in SARS-CoV-2 infections: State of the art

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SUMMARY

OBJECTIVE: *The scientific community is constantly assessing the clinical and laboratory manifestations of COVID-19 in the organism. In view of the fragmentation of the large amount of information, knowledge gaps in relation to laboratory markers, and scarcity of papers in Portuguese, we propose a Literature review on laboratory changes observed in patients infected with SARS-CoV-2.*

METHODS: *Analysis of articles published between December 2019 and May 2020 on the PubMed and SciELO databases. The articles were identified, filtered, and evaluated based on the approach to the subject, language, and impact. Then, the articles were subjected to a thorough reading, in full, by 4 (four) independent researchers.*

RESULTS: *Leukopenia and lymphopenia were included in most studies, even in case definitions. Platelet count and platelet-lymphocyte ratio, at peak platelet, were associated with advanced age and longer hospital stay. Eosinopenia showed a sensitivity of 74.7% and specificity of 68.7% and, together with increased CRP, these are one of the future prospects for screening for disease. A high level of procalcitonin may indicate bacterial co-infection, leading to a worse prognosis. COVID-19 manifests itself with increased levels of many inflammatory markers such as IL-1, IL-2, IL-6, IL-7, IL-12, IP10, IFN-γ, MIP1A, MCP1, GSCF, TNF-α, and MCP1/CCL2, as well as LDH, ESR, D-dimer, CK, ALT, and AST.*

CONCLUSION: *There is a need for further studies on the new SARS-CoV-2. So far, there is no consensus regarding laboratory findings and their usefulness, whether as a prognostic marker, mortality, or disease severity.*

KEYWORDS: *Coronavirus Infections. Betacoronavirus. Blood Cell Count. Leukocyte Count.*

INTRODUCTION

In December 2019, the first cases of a severe acute respiratory infection of unknown etiology by then appeared in the city of Wuhan, the capital of the Hubei province, in China, the first epicenter of the current pandemic[1,2]. After further investigation, it was found that many of the patients had a common exposure to the wholesale seafood market of Huanan, known for the trade of live animals[1]. Shortly, the agent

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responsible for the disease was identified. The now called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused by the 2019 novel coronavirus (2019-nCoV), which quickly spread throughout China, as well as the world, having reached by April a total of 823,626 cases and 40,598 deaths[1,3].

The coronaviruses are single-stranded RNA viruses, enveloped, that measure around 60nm to 140nm in diameter and feature projections on its surface, hence the name coronaviruses, in allusion to a crown. Other viruses of this same family also circulate in humans and usually cause respiratory syndromes, some examples are the HKU1, NL63, 229E, OC43, MERS-CoV, and SARS-CoV[1,4]. SARS-CoV-2 is the agent responsible for COVID-19, it is 50% genetically compatible with MERS-VOC and 79% compatible with SARS-CoV[2].

The clinical manifestations of this new disease have not been not fully established yet since they vary from mild symptoms to severe pneumonia with extensive alveolar damage, which may result in death[5,6]. The most commonly reported symptoms are fever, dry cough, myalgia, fatigue, dyspnea, and even headache, diarrhea, hemoptysis, coryza, as well as productive cough[5,7]. The fatal cases were, in general, of middle-aged and elderly patients with pre-existing conditions (oncologic surgery, cirrhosis, hypertension, heart disease, coronary disease, diabetes, and Parkinson)[6].

The laboratory findings of COVID-19 show the results of the virus' mechanism of attack to host cells. In this sense, the phenomenon known as amplification of the immune response was confirmed in multiple viral infections. In it, there is a cellular uptake of virus-antibody complexes after virus interaction with FcR, FcγR, or other receptors, resulting in a more objective infection in the target cells. In addition, the interaction of FcγR receivers with the complex of anti-virus S-protein (anti-S-IgG) neutralizing antibodies can facilitate both inflammatory responses and the persistent viral replication in patients' lungs[8].

Since this is a recent pandemic, the scientific community is still evaluating the clinical and laboratory consequences of the infection in the body. Thus, considering the fragmentation of larges amounts of information, the gaps in knowledge regarding laboratory markers in COVID-19, and the scarcity of studies in the Portuguese language, we propose a comprehensive and dynamic literature review on laboratory alterations observed in patients infected by SARS-CoV-2.

METHODS

The review selected articles published from 31 December 2019 until 1 May 2020, indexed in the following databases: PubMed (US National Library of Medicine National Institutes of Health) and SciELO (Scientific Electronic Library Online). The descriptors (MeSH) used were: *"2019 novel coronavirus" or "2019-nCoV" or "COVID-19"*. We considered eligible articles in the English language whose summary included laboratory findings from patients with confirmed positive results by molecular testing for SARS-CoV-2 infection. The references from the studies identified were also analyzed to detect additional studies. Thus, we selected 19 (nineteen) articles based on their approach to the subject and impact. Then, the articles were subjected to a thorough reading, in full, by 4 (four) independent researchers.

Hemogram alterations

Among the first laboratory findings reported in patients diagnosed with COVID-19 is a reduction in the number of white blood cells (leukopenia), which varied, between the studies, from 9.1% to 33.7%[3,4,7,9,10], a reduction in the number of lymphocytes (lymphopenia)[3,4,7,9-12], and, later, of eosinophils[13,14].

The percentage of patients with lymphopenia in the studies discussed[3,4,7,9,10] ranged from 35.3% to 82.1%, the highest value presented by Guan et al.[9], from a study involving 1099 patients. Therefore, lymphopenia is among the most common laboratory findings, illustrating the apoptosis activation mechanism and the signaling pathway of the P53 pathway, induced by SARS-CoV-2 in lymphocytes, providing a decreased immune response to the virus[2,7,15,16]. Indeed, the (Chinese) guidelines began to include lymphopenia and leukopenia in their case definitions. Still, in regard to lymphopenia, numbers below 1000 would be associated with more severe presentations of the disease[1,17]. It was also reported that non-surviving patients developed lymphopenia and leukocytosis more often, along with abnormal values of D-dimer, blood urea nitrogen, and creatinine[18].

The work by Chen et al.[3] analyzed, through a series of 30 cases, the dynamic alterations in the number of platelets during the treatment of COVID-19 patients. The univariate analysis of the study showed that age, platelet peaks, and the platelet-lymphocytes ratio (PLR), during the platelet peak, were influencing factors in severe patients, while a multivariate analysis showed that the PLR value during the

peak was an independent influencing factor in severe patients. The maximum number (mean) of platelets or peaks during the treatment in severe patients was 392 × 10^9/L, significantly higher than the 301 × 109/L of non-severe patients (P=0.047). The platelets/lymphocytes ratio (PLR) of 626 severe patients was significantly greater than the 262 (P=0.001) of non-severe patients. The platelet peaks were also associated with more advanced age and longer hospitalization (P<0.005). This could be related to the cytokines storm phenomenon. In this way, based on the absolute values, the fact that the levels of lymphocytes and platelets are sensitive indicators that reflect the control of infection and inflammation, and the results presented, the PLR could be used in the monitoring of COVID-19 patients.

With respect to eosinopenia, it is important to mention the retrospective comparative study by Li et al.[13], which divided 989 patients based on the nucleic acid test of the polymerase chain reaction for SARS-CoV-2 infection into two groups, one positive and one negative for SARS-CoV-2. The work confirmed some laboratory findings already well described, such as leukopenia, lymphopenia, and increased PCR. However, among the most interesting results, eosinopenia presented a sensitivity of 74.7% and specificity of 68.7%, with an area under the curve (AUC) of 0.717, and the combination of eosinopenia and increased ultra-sensitive C-reactive protein (us-PCR) presented a sensitivity of 67.9% and specificity of 78.2% (AUC of 0.730). Thus, according to the authors, eosinopenia or the combination of eosinopenia and increased us-PCR in the diagnostic parameters recommended by the COVID-19 guidelines would improve predictive and discriminatory capacity and, therefore, could efficiently screen patients suspected of COVID-19, changing, thus, the strategic parameters for managing the disease since it would also decrease the medical resources necessary for molecular and imaging tests.

The eosinophil count is among the laboratory findings that showed a potential for predicting the progression of the coronavirus since, as concluded by some studies, almost all patients presented eosinopenia in the first week of hospitalization. However, the time for eosinophil recovery, in mild patients, was less than that in severe cases; thus, this suggests that a lower and ascending eosinophil count can be a sign of progression and recovery of COVID-19, respectively[14].

The platelet count is usually normal or slightly low[1], but the presence of thrombocytopenia ranged from 5.0% to 36.2% in the studies analyzed[3,4,7,9,10]. As for the red series, Huang et al.[7]reported anemia as one of the most common complications found in COVID-19 patients.

Procalcitonin and troponin I

Increased values of procalcitonin, creatinine, and troponin I are uncommon in new coronavirus infections[7,9,10]. However, in the study by Huang et al.[7], 12% of the cases were diagnosed with myocarditis; thus, the level of high-sensitivity troponin I was significantly higher in those patients. Procalcitonin is a pro-hormone associated with infectious diseases, however, most COVID-19 patients present normal values of serum procalcitonin[1,4,7,11,12]. Thus, a high level of procalcitonin could indicate a co-bacterial infection and, consequently, worse prognosis[1.19]. Following this same line of reasoning, it was observed that the rate of patients with abnormal values admitted to the ICU was three times higher than those with normal values (75% vs. 22%; p <0.001)[18].

Cytokines and cytokine storms

Patients with SARS and COVID-19 have similar patterns of inflammatory damage. In the serum of patients diagnosed with SARS, there are increased levels of pro-inflammatory cytokines {for example, interleukin (IL)-1, IL-6, IL12, interferon-gamma (IFN-γ), interferon γ–induced protein-10 (IP10), macrophage inflammatory proteins 1A (MIP1A), and monocyte chemoattractant protein-1 (MCP1)}, which are associated with lung inflammation and severe pulmonary injury[20].

In addition, other cytokines, such as IL-7, IL-2, granulocyte-colony stimulating factor (GSCF), tumor necrosis factor-alpha (TNF-α), and monocyte chemoattractant protein 1 (MCP1/CCL2) also had higher plasma levels in COVID-19 patients, when compared to healthy adults[7]. Unexpectedly, some anti-inflammatory cytokines such as IL10 and IL4 were also increased in these patients[7], an unusual phenomenon in the acute phase of a viral infection. The same study highlights that ICU patients have a significantly higher level of GSCF, IP10, MCP1, MIP1A, and TNF-α than those not in the ICU, suggesting that the phenomenon of "cytokine storms" may aggravate the disease, so it could be associated with the progression of pneumonia/respiratory failure[3.7].

Other laboratory findings

It is worth mentioning other laboratory findings considered common by some authors, such as the prolonged duration of prothrombin and increased lactate dehydrogenase enzyme (LDH)[1,4]. There are also mentions to increased the values of serum ferritin, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), D-dimer, creatine kinase (CK), alanine transaminase (ALT), aspartate transaminase(AST), total bilirubin, and reduced values of albumin[3,4,7,9,10,21]. High ferritin, ALT, and AST could be the result of liver injury due to an affinity of the virus with the liver in the advanced stage of disease[3].

The plasma D-dimer is a fibrin degradation product, which has a cross-reaction with it and, when dosed by the quantitative ELISA method, has been shown to be highly sensitive (above 99%) in cases of deep venous thrombosis and nonmassive pulmonary thromboembolism (PTE), with a cutoff value of 500 μg/L; therefore, values lower than 500 μg, virtually exclude PTE.[22]

However, the specificity of the fibrin for PTE is very low since its production is increased in situations such as cancer, inflammation, infection, necrosis, and in post-operative periods in general. Therefore, levels above 500 μg/L have a very low predictive value for PTE and are unable to confirm the disease 22· However, in the current pandemic context, a study conducted by Garcia-Olivé et al.[23], pointed out that patients diagnosed with pneumonia caused by COVID-19 and higher levels of D-dimer were associated to a greater probability of developing TEP 3, 6, 9 and 12 days after the identification of the D-dimer levels with an odds ratio (OR) of 1.7, 2.0, 2.4, and 2.4, respectively.

Tang et al.[24] also found that abnormal coagulation parameters were more frequent in patients who died (n=21) than in those who survived. Specifically, the values of PT, D-dimer, and fibrinogen were 1.14, 3.5, and 1.9 times higher in non-survivors than in survivors, respectively. In general, 71.4% of the patients who died met the criteria for disseminated intravascular coagulation (DIC), in comparison with only 0.6% of those who survived[24]. Thus, some authors suggest that an evaluation for DIC should be regarded as a routine part of COVID-19 patient monitoring[18].

The lactate dehydrogenase (LDH) enzyme is another marker that we highlight, since a study suggested, through multivariate regression, that LDH was an independent risk factor for COVID-19 based on a comparison with influenza A (H1N1)[25]. In this study, it was concluded that the LDH was an independent predictor of death in healthy adults and a risk factor for death in patients with cardiovascular diseases, reflecting the direct damage to myocardial cells[25].

Finally, as expected, patients admitted to intensive care units (ICUs) feature more laboratory abnormalities than those who are not[4,7]. Still regarding patients in need of intensive care, we stress the importance of the Italian study by Zangrillo et al.[17], which included 73 ICU patients under mechanical ventilation, i.e., severe patients, in order to identify predictors of early mortality. The analysis found a curious laboratory profile of lymphopenia (average of 770 per mm3; CI: 580-1000 per mm3), hyper inflammation with PCR (average of 184.5 mg/dL; CI: 108.2-269.1 mg/dL), and D-dimer (average of 10.1 μg/m; CI: 5.0-23.8 μg/m).

CONCLUSION

It is evident, therefore, that further studies are needed on the new SARS-CoV-2 and its interactions with the body. The clinical alterations it causes, as well as the laboratory findings resulting from the infection, must be better described. It is also important to investigate the laboratory profile not only of symptomatic patients but also of the little-studied asymptomatic ones. In addition, there are still gaps in our knowledge, such as the contradictory increase of anti-inflammatory cytokines, the usefulness of the PLR, and the curious normal values of procalcitonin in patients with the disease.

In short, despite the limitations of the current scientific literature (small samples, most of the studies involving the same population [Chinese], mostly Chinese operational definitions and reference values, and many clinical studies in progress), it would be utopian to expect the quick identification of new markers of the new coronavirus infections, predictors of severity, and mortality, as well as algorithms and guidelines based on laboratory findings, thus determining new approaches.

RESUMO

OBJETIVO: *A comunidade científica avalia a todo momento, as manifestações clínicas e laboratoriais da COVID-19 no organismo e, em vista da fragmentação da grande quantidade de informações, lacunas de conhecimento em relação aos marcadores laboratoriais e escassez de trabalhos em português, propomos uma revisão de Literatura sobre alterações laboratoriais observadas em pacientes infectados por SARS-CoV-2.*

MÉTODOS: *Análise de artigos publicados entre dezembro de 2019 a maio de 2020 nas plataformas PubMed e SciELO. Os artigos foram identificados, filtrados e avaliados com base na abordagem ao assunto, idioma e impacto. Depois, os artigos foram submetidos a uma minuciosa leitura, na íntegra, por 4 (quatro) pesquisadores independentes.*

RESULTADOS: *A leucopenia e a linfopenia constaram na maioria dos trabalhos, presente até em definições de caso. A contagem de plaquetas e a razão plaquetas-linfócitos, no pico plaquetário, foram associados à idade avançada e maior tempo de hospitalização. A eosinopenia apresentou sensibilidade de 74,7% e especificidade de 68,7% e, juntamente com aumento da PCR, são uma das perspectivas futuras de triagem para doença. O alto nível de procalcitonina pode indicar uma co-infecção bacteriana, levando a pior prognóstico. A COVID-19 se manifesta com níveis aumentados de muitos marcadores inflamatórios como IL-1, IL-2, IL-6, IL-7, IL-12, IP10, IFN-γ, MIP1A, MCP1, GSCF, TNF-α e MCP1/CCL2, bem como LDH, VHS, dímero-D, CK, ALT e AST.*

CONCLUSÃO: *Há necessidade de estudos adicionais sobre o novo SARS-CoV-2. Até agora, não há unanimidade em relação aos achados laboratoriais e sua utilidade, seja como marcador prognóstico, de mortalidade, ou de severidade de doença.*

PALAVRAS-CHAVE: *Infecções por Coronavirus. Betacoronavirus. Contagem de células sanguíneas. Contagem de Leucócitos.*

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