Chapter

Usefulness of the Hemogram in COVID-19

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Abstract

SARS-CoV2 infection has devastating consequences on healthcare systems and has caused 3 million deaths by April 2021. Identifying patients at risk of death is a priority. Moderate–severe COVID-19 cases seem to associate a cytokine release that follows endothelial injury, triggering a hyperinflammatory and procoagulant state in which leukocytes and platelets are protagonists. Our group has published some reports about the usefulness of the hemogram in COVID-19. Hemogram-derived ratios, mainly the neutrophil-to-lymphocyte ratio (NLR) and the novelty neutrophil-to-platelet ratio (NPR), obtained on admission and their rate of change during hospitalization, can easily detect patients with high risk of mortality. Hemogram is a tool available to all hospitals and analyzing the hemogram-derived ratios would provide much more information than could be extracted by evaluating the counts in isolation. We now know that in COVID-19 it is essential to start early anti-inflammatory treatment when patient deteriorates and the hemogram could be a good indicator of this situation. More comprehensive studies are needed to determine how useful these hemogram-derived ratios and prognostic scores are. In the next chapter we will present information related to this aspect as well as our group's research on the usefulness of the hemogram in COVID-19.

Keywords: COVID-19, neutrophil-to-platelet ratio, NPR, neutrophil-to-lymphocyte ratio, NLR, hemogram-derived ratios

1. Introduction

COVID-19 is a systemic disease, in which all organs can be affected. Several studies have emphasized an anomalous immune response as the starting point for hypercoagulability phenomena, endothelial damage and macro- and microthrombosis, which would trigger life-threatening consequences in patients. White blood cell populations (monocytes, lymphocytes and neutrophils) play a crucial role in the systemic inflammatory response and platelets have a direct function in the thrombotic response.

Differential blood cell counts can be measured simply, are cost-effective and reliable, and therefore can be used as markers of severity of the immune and inflammatory, and even the procoagulant response. In this context, white blood cells and platelets as circulating biomarkers involved in inflammatory and

thrombotic responses could potentially predict clinical outcomes of patients with COVID-19.

Various hemogram parameters, including hemogram-derived ratios, have been used to try to identify patients with worse prognosis for COVID-19. In the following chapter the reader will find information related to this aspect as well as our group's research on the usefulness of the hemogram in COVID-19.

2. Pathophysiological basis for the potential usefulness of the blood count in COVID-19

The clinical presentation of COVID-19, ranges from a mild, self-limited form of the disease to multiple organ failure [1–4]. In the most severe cases, the disease can lead to severe viral pneumonia with dyspnea and hypoxemia that can evolve into severe respiratory distress syndrome, heart failure, obstructive thromboinflammatory syndrome, septic shock and multi-organ failure. This rapidly progressive deterioration causes the disease even fatal in some patients [5–11].

Several studies have emphasized an anomalous immune response as the starting point of an obstructive thrombo-inflammatory syndrome in which all organs can be affected, especially vital organs such as the kidney or the heart, with the incidence of pulmonary embolisms being very high in COVID-19 patients [12–14]. The most severe middle-aged patients suffered more localized lung damage and coagulopathy [14].

Some of the variables that have shown significant correlation with poor outcomes in COVID-19 include male sex, older age, smoking status, and the coexistence of comorbidities such as obesity, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, hepatitis B infections and malignancy [1, 11].

Analytical parameters have also been widely used in early evaluation and monitoring of COVID-19 patients. Many of these parameters, specifically derived from white blood cell or platelet count values, provide information on both immunological status and hemostasis in response to SARS-CoV-2 infection.

In fact, the host's inflammatory response to SARS-CoV-2 infection appears critical in clinical evolution of COVID-19, and blood cell interactions are essential in the pathophysiology of inflammation, immune responses and hemostasis in this setting.

These interactions are complex, and it is often difficult to discriminate the specific roles of each cell type in the different phases of the same disease. Platelets are the main mediators of hemostasis while leukocytes are responsible for the immune responses.

White blood cell populations (monocytes, lymphocytes and neutrophils) are the main protagonists in the systemic inflammatory response to severe infection, injury, trauma and shock and therefore can be used as markers of this response [15]. Neutrophils are the most abundant white blood cells in circulation and represent the first line of innate immune defense, playing a fundamental role [7]. Furthermore, when this cell type is active, it has migratory capacity from the venous system to the affected organ or systems [11].

Accumulating evidence suggests that a portion of patients presenting with severe COVID-19 may have an underlying hyperinflammatory response that drives a cytokine release storm resulting in multiorgan failure and death [16]. A novel form of microvascular obstructive thromboinflammatory syndrome has been proposed as the pathophysiology underlying this hyperinflammatory response. Following SARS-CoV-2 infection, CD4+ T lymphocytes are rapidly activated to

become pathogenic T helper 1, cells that produce cytokines that stimulate inflammatory CD14 + CD16+ monocytes generating IL-6 expression and accelerating the inflammatory process [17]. The inflammatory response may stimulate neutrophil production and even accelerate lymphocyte apoptosis.

Autopsies of patients affected by COVID-19 revealed a significant infiltration of neutrophils in the pulmonary capillaries with extravasation towards the alveolar lumen. This existence of acute capillaritis together with the presence of tracheal neutrophilic mucositis demonstrates the existence of a general inflammation of the airways [7].

Neutrophils can release large amounts of oxygen free radicals, which induce cell damage and release of viral particles from cells. Antibody-dependent cells can directly destroy the virus by exposing the viral antigen and thus activating cell-specific and humoral immunity. Neutrophils are also capable of producing large amounts of cytokines and signaling molecules such as endothelial growth factors (VEGF). Two of these factors, VEGF-A and VEGF-C, present significantly higher values in COVID-19 patients [11]. The accumulation of neutrophils associated with endothelial cell infection in COVID-19 disease induces endothelitis in different organs, thus contributing to systemic damage due to hypoxic microcirculation failure [7]. Increased neutrophils is an important risk factor and is closely related to increased patient severity, the development of acute respiratory syndrome (ARDS), and death in COVID-19 patients [18].

Infected pulmonary macrophages produce TNF-α and interleukins that cause T-cell apoptosis and lymphocyte recirculation, with massive recruitment into inflamed tissues [19, 20]. In addition, it is known that SARS-CoV-2 can directly infect lymphocytes, which have the angiotensin-converting enzyme 2 (ACE 2) receptor, so the virus can cause a decrease in their count, especially TCD8 + and TCD4 + lymphocytes [21, 22]. This triggers global lymphopenia, common in patients with severe COVID-19. It has been shown that the lower the lymphocyte count and the longer the duration of lymphopenia, the more severe the condition of infected patients and the worse the prognosis [19, 20].

Dysregulated immune cell responses are thought to play a notable role in the severity of disease [23]. Severe inflammatory responses result in a weak adaptive immune response, which translates into an imbalance of the immune response.

Several studies have shown that patients with COVID-19 who have higher levels of inflammatory cytokines and chemokines have greater disease severity, suggesting the involvement of cytokine storm in severe forms of the disease [1, 24]. This uncontrolled cytokine production, which increases as the infection worsens, provides the setting for SARS-CoV-2 pathogenesis leading to viral sepsis, tissue damage, disseminated intravascular coagulation, shock and even multi-organ failure. Proinflammatory cytokines induce apoptosis in lung epithelial cells, dendritic cells and macrophages, which impairs the pulmonary microvascular barrier and alveolar gas exchange. They increase vascular permeability, as well as the amount of fluid and inflammatory cells in the alveoli, causing dyspnea and respiratory failure [24, 25].

It has been hypothesized that an endothelial thromboinflammatory syndrome is triggered after alveolar viral damage [26]. SARS-CoV-2 uses the cell surface ACE 2 receptor to enter the interior of cells. ACE 2 is expressed in several organs, including endothelial cells [21, 22]. It has been reported that SARS-CoV-2 can infect genetically modified human blood vessel organoids in vitro, and the involvement of endothelial cells in the vascular beds of different organs has also been demonstrated in necropsies performed on deceased COVID-19 patients [27, 28].

Endothelial cell damage may be an important trigger of cytokine discharge, and moderate and severe COVID-19 cases appear to be associated with a large release of cytokines, leading to a hyperinflammatory and procoagulant state. Such

inflammation, associated with the disproportionate cytokine storm, spreads widely through the systemic circulation, affecting different organs with high mortality [29].

This procoagulant state is associated with thromboembolic phenomena, such as deep vein thrombosis and pulmonary thromboembolism, which carry a worse prognosis. Anatomopathological studies of the lungs of patients with COVID-19 have shown frequent and systematic findings of thrombotic microangiopathy and hemorrhage [30, 31].

This new form of microvascular obstructive thromboinflammatory syndrome has been proposed as the pathophysiological basis underlying this hyperinflammatory response. This endothelial thromboinflammatory syndrome can progressively involve the microvascular bed of several vital organs, leading to multiple organ failure and death [26].

In addition, individuals with pre-existing endothelial dysfunction and therefore with a more active base inflammatory state, could lead to worse evolution in COVID-19. It has been observed that those patients affected by COVID-19 and with cardiovascular diseases had a greater probability of suffering myocardial injuries than those who did not present this type of previous injuries. Furthermore, those patients with chronic obstructive pulmonary disease (COPD) had a greater probability of suffering pulmonary coinfections and septic shock. Moreover, patients with previous kidney disease are also susceptible to developing COVID-19-induced worsening of kidney disease. The presence of these comorbidities may have increased mortality independently of COVID-19 infection as a result of the worsening of comorbidities induced by the viral infection rather than by the direct damage produced by SARS-CoV-2 [14].

In this context, white blood cells and platelets would have a direct role in this inflammation and in the thrombotic response; therefore, circulating biomarkers representing inflammation and immune status could potentially predict clinical outcomes of COVID-19 patients [11, 32].

Following these findings, routine blood tests and differential white blood cell counts are easy to obtain at most healthcare centers and are affordable and cheap markers for predicting a worse prognosis in COVID-19.

Several studies have reported the results of blood tests in patients with COVID-19, and most severe cases present low lymphocytes counts, higher leukocytes counts and hemogram-derived ratios, as well as lower percentages of monocytes, eosinophils and basophils [24]. Some of these inflammatory markers have been evaluated and found to correlate with worse prognosis, including peripheral white blood cell count and hemogram-derived ratios.

3. Hemogram-derived ratios in COVID-19

The hemogram-derived ratios are parameters which amplify the value of neutrophils, platelets and lymphocytes and could be useful to predict prognosis and severity of the disease. Several hemogram-derived ratios as neutrophil-to-lymphocyte ratio (NLR), derived NLR ratio (dNLR) (neutrophil count/leukocyte count−neutrophil count), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio have been used as inflammatory markers of COVID-19 [11, 32–34].

3.1 Neutrophil-to-lymphocyte ratio (NLR)

An available marker of great value for measuring the inflammatory status of an individual is the NLR, an easily measurable parameter that is obtained from a routine blood test. It is the ratio of the absolute neutrophil count to the absolute lymphocyte count of a routine blood count [33, 35, 36].

It has been proposed as a prognostic marker of severity in many pathologies such as oncological processes, septic shock, infectious diseases, intracranial hemorrhage and cardiovascular disease among others [35, 36].

Moreover, NLR appears to be an indicator of endothelial dysfunction and an important predictor of cardiovascular mortality [23, 24].

The endothelial dysfunction could be one of the aggravating factors of SARS-CoV-2 disease and would explain the evolution of the disease towards multiple organ failure [37–40]. Several studies have been published, incorporating NLR as a marker of poor prognosis in patients with COVID-19 [8, 11, 33, 41, 42].

The normal values of this quotient in an adult population, excluding the geriatric population, are around 0.78 and 3.5. When the NLR result exceeds the normal maximum value, the probability of the disease going from a mild–moderate to a severe state dramatically increases.

A higher NLR value at admission is related to mortality in COVID-19, since high values have been observed at the beginning of admission in patients who did not survive [37]. This is because in more severe patients, the inflammatory response stimulates neutrophil production and therefore the neutrophil count is higher, while this response accelerates lymphocyte apoptosis and the lymphocyte count is low, and therefore the NLR value increases.

Our group has investigated the usefulness of this ratio being one of the first groups to publish on the implications of this ratio and its relationship with worse prognosis in COVID-19. In a small cohort of patients, we demonstrated how the evolution of NLR in terms of rate of increase and Peak NLR was associated with worse outcomes in COVID-19 with higher risk of ICU admission or death [38].

Subsequently, in a cohort of more than 2000 patients, we demonstrated that NLR is associated with in-hospital mortality as it is higher at baseline hospital admission and maintains significance after multivariable adjustment [43].

Moreover, patients requiring ICU admission had significantly higher NLR values at the time of hospital admission [44].

3.2 Platelet-to-lymphocyte ratio (PLR)

Some studies demonstrate the ratio of platelet count to lymphocyte count, called PLR, as a reliable marker of immune-mediated, metabolic, prothrombotic and neoplastic diseases.

Its use in combination with other complementary hematological ratios, in particular NLR, provides additional information on the degree of disease activity and helps to monitor the response to anti-inflammatory treatments. It could even help in the early detection of comorbidities that develop in the course of disease treatment [45–47].

PLR primarily reflects the level of systemic inflammation that translates megakaryocyte activity in the hematopoietic tissue of the bone marrow, an important component in thrombosis. It also plays a very important role in the inflammatory response by promoting the recruitment of neutrophils and other inflammatory cells to the site of injury.

This ratio reflects both aggregation and inflammatory pathways and is therefore considered by some authors to be more valid for predicting inflammatory pathology than platelet or lymphocyte counts alone [11]. However, relationship between PLR and mortality has been less explored.

It has been postulated that PLR may reflect the degree of cytokine release, which could be a useful indicator of the clinical course of COVID-19 patients [48]. SARS-CoV-2 infection causes a cytokine storm in body fluids, aggravating the patient's inflammatory response and stimulating platelet release. Some authors consider that platelet number and its dynamic changes during the course of COVID-19 and

treatment may correlate with cytokine storm, and consequently, with disease severity and prognosis [48].

Our group has also investigated the usefulness of this ratio in COVID-19 and we observed that patients who died presented significantly higher PLR compared with patients who survived at admission [43], like patients requiring ICU admission [44], but they did not maintain significance after more complex model of multivariable adjustment.

3.3 Systemic immune-inflammation index (SII)

The systemic immune-inflammation index (SII) is a hemogram-derived ratio defined as the count of neutrophils multiplied by the count of platelets and divided by the count of lymphocytes.

SII has recently been proposed as a prognostic indicator in the follow-up of patients with sepsis [49] and cancer patients [50, 51] as an index defining the instability in the inflammatory response.

This quotient derived from the hemogram has also been studied by our group in patients affected by COVID-19 and, like PLR, SII on admission is significantly higher in COVID-19 patients who died and required admission to the ICU, but it did not maintain statistical significance after multivariate adjustment [43, 44].

3.4 Neutrophil-to-platelet ratio (NPR)

The modulatory interaction between neutrophils and platelets has previously been described [52] and based on the biological plausibility of higher total neutrophils count and lower total platelets count observed among the most severe COVID-19 cases compared to more mild ones, we have investigated the utility of a novel parameter, the neutrophil–platelet ratio (NPR).

NPR is the ratio between the count of neutrophils (x 10^9 cells/L) and the count of platelets (x 10^{11}cells/L), and may be useful in signaling a combination of hyperinflammatory response and microvascular occlusion that has been identified in moderate to severe COVID-19 cases [26, 53].

We hypothesize that a damaged and activated endothelium may increase the permeability and release of cytokines that would initiate chemotaxis of inflammatory cells and also recruit other blood cells.

In this context, activated platelets and neutrophils play a determining role in microvascular occlusion during the thromboinflammatory phase of the disease [54]. These findings were observed in the most severe COVID-19 cases who died, especially higher neutrophil and lower platelet counts.

Our results have shown that NPR levels were significantly associated with in-hospital mortality due to COVID-19 and their association remained significant even after multivariable adjustment.

Also, higher levels of NPR at admission are related to higher risk of ICU admission in COVID-19 patients [43, 44].

We are the first group in the world reporting the usefulness of this hemogram-derived ratio in a disease and we believe that this novel finding merits further investigation.

3.5 Incorporation of rates of change of hemogram-derived ratios

Our group has also studied the rate of change in the ratios derived from the blood count during the first days of hospitalization in patients affected by COVID-19.

The rate of increase has been shown to be a useful marker of severity and is associated with mortality.

Undoubtedly, these rates of change could be affected by the course of COVID-19 and the treatments applied, but we hypothesized that some of these rates could be a valuable parameter in the control of patients without additional risk factors to assess modifying the treatment [38, 43, 44].

3.6 Incorporation of hemogram-derived ratios into clinical judgment nomograms

In most cases, the first assessment for a COVID-19 case takes place in the emergency department, where it is routine clinical practice to carry out a full blood panel.

Based on the usefulness of the hemogram-derived ratio, we have developed the Risk Score for Predicting In-Hospital Mortality in COVID-19 (RIM Score COVID) [53].

We have developed four models: two with NLR, the ratio more widely reported, and two with NPR, the novel hemogram-derived-ratio proposed by our group. No significant differences were found between NLR and NPR models; however, models using the NPR ratio showed more robustness in more complex multivariate analyses.

The RIM Score COVID includes following variables at hospital admission: age, sex, oxygen saturation, level of C-reactive-protein, NPR and NLR.

The AUC of models including NLR and NPR were evaluated for predicting in-hospital mortality by COVID-19 and both performed similarly in the validation cohorts: NLR 0.856 (95% CI: 0.818–0.895), NPR 0.863 (95% CI: 0.826–0.901).

Moreover, we have developed two models incorporating the rate of changes of both hemogram-derived ratios during the first week after admission, called Velocity of NLR (VNLR) and Velocity of NPR (VNPR).

The accuracy of the models were also evaluated for predicting in-hospital mortality by COVID-19 and the predictive ability of in-hospital mortality in both models improved slightly in the validation cohorts with respect to the values obtained at admission: VNLR 0.885 (95% CI: 0.885–0.919), VNPR 0.891 (95% CI: 0.861–0.922).

According to our results, the RIM Score COVID models are useful for predicting the risk of in-hospital mortality from COVID-19.

The proposed RIM Score is a simple and widely available tool that can help identify patients at risk of fatal outcomes.

The parameters used in the nomogram are objective, easy to obtain and reproducible in most healthcare facilities without additional cost or need for additional laboratory equipment.

These assessments provide a highly accurate predictive value of in-hospital mortality risk from COVID-19 [53].

4. Conclusions

The hemogram is an easily measurable, readily available, cost-effective and reliable test that could be very useful in establishing the risk of in-hospital mortality on hospital admission and in guiding therapeutic decisions in patients with COVID-19.

In this sense, the hemogram is a tool available to all healthcare centers that do not have the technical and material means to perform complex immunological studies, which usually involve late results.

The combination of hemogram parameters and blood cell count ratios in COVID-19 patients could be a useful combined indicator of host immune and inflammatory status.

The ratios derived from the hemogram at the time of hospital admission and its increasing trend during the first days of hospitalization have shown their value in identifying patients with COVID-19 who have a worse evolution and could be useful as prognostic markers of the disease.

The NLR and the novelty NPR have been shown to be independent markers of mortality and worse prognosis in patients with COVID-19. These ratios should be included in future prospective studies and it would be advisable to start using them by physicians in the first evaluation of patients with COVID-19 in the emergency department to demonstrate their clinical utility.

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Conflict of interest

Salvador I. Garcia-Adasme has received private founds by HM Hospitales to course his doctoral studies in CEU International Doctoral School – CEINDO, CEU-San Pablo University.

The remaining authors declare no conflicts of interest.

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