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Predictable severity biomarkers in Covid-19

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Abstract

Introduction: The recorded studies suggest that there is clear evidence-based association between various laboratory biomarkers and COVID-19 disease severity. These marker levels reflect the intensity of the cytokine-mediated hyperinflammatory response, which is strongly associated with a poor outcome of SARS-CoV-2 infection.

Conclusions: C-reactive protein is not only a systemic inflammatory marker, but also an important regulator of inflammatory processes. The level of this protein is positively correlated and can be widely used to predict the severity, prognosis and mortality in COVID-19 patients, additionally to vital signs monitoring, supportive care, oxygen therapy, ventilation and circulatory support. Procalcitonin is an indicator of disease severity, which can facilitate timely clinical decision-making, and determination of procalcitonin levels during COVID-19 patients' follow-up, as well as being used in assessing risk, predicting prognosis, and improving patient survival. The assessment of hematological laboratory parameters upon admission, which help in differentiating between severe and non-severe cases, high-risk and low-risk cases of mortality, allows raising awareness, monitoring and timely treatment of patients with COVID-19, as well as their early improvement of clinical condition. Inflammatory biochemical and hemocytometric measures are feasible, easily interpretable, and widely available biomarkers in most healthcare settings, favorable for being used in treatment and severity determination, in predicting clinical outcomes, and in the prognosis of patients with COVID-19. However, the assessment of the accuracy of these biomarkers needs to be determined in further more relevant worldwide studies, showing a more precise design, more accurate performance, and having larger sample sizes.

Key words: COVID-19, SARS-CoV-2, C-reactive protein, procalcitonin, biomarkers, severity prediction.

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Introduction

The 2019 coronavirus disease (COVID-19) pandemic remains a scientific, medical, and social challenge. The complexity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) lies in the unpredictable clinical course of the disease, which can develop rapidly, causing serious complications and death [1, 2]. The wide clinical range of SARS-CoV-2 infection varies from asymptomatic and mild to severe, critical and fatal. Asymptomatic forms account from 20% to 75% of confirmed cases of COVID-19 among overall population [3]. Most of the affected patients (81%) are mild and moderate cases, approximately 19% of patients develop severe (14%) or critical (5%) forms, the latter two being associated with respiratory failure, acute respiratory distress syndrome (ARDS), multiple organ failure syndrome, in-hospital care followed by poor prognosis and high mortality rates [4, 5].

Up to 30% of COVID-19 patients require hospital admission, whereas the disease was observed to progress in 19.6% of moderate cases, in 27.8% of severe cases, and in 66.7% of critical cases during the hospital stay. About 17-20% of patients are hospitalized within the intensive care unit (ICU). The overall mortality of COVID-19 patients is approximately 2.3%, and the mortality of patients admitted to the ICU is 50-61.5% [4-9].

Given the wide range of SARS-CoV-2 infection severity, it is critical to determine some laboratory biomarkers for risk stratification and outcome prediction in patients with COVID-19, as well as for identifying the patients who might provide objective criteria for disease evolution or rapid diagnosis of a condition resulting in severe complications and death, for supporting the clinical decision-making and the appropriate allocation of medical resources [7, 10-18].

Although, efficient indicators that predict the severity

and progression of SARS-CoV-2 infection are not yet available, numerous studies have estimated various biomarkers (C-reactive protein, interleukin-6, lactate dehydrogenase, albumin, procalcitonin, white blood cell count, lymphocyte count, platelet count, neutrophil-lymphocyte ratio, C-reactive protein-albumin ratio, D-dimer, ferritin, cardiac troponin, renal biomarkers, etc.) to determine the possibility of predicting the progression and clinical outcomes of the condition, to evaluate the correlation of these biomarkers with disease severity and deaths caused by COVID-19 [2, 14, 15, 19-24].

The above listed laboratory biomarkers may be widely used in monitoring and predicting the disease outcomes and prognosis. However, the dynamic changes, the specificity and the sensitivity of these parameters for the diagnosis of SARS-CoV-2 infection and their correlation with the COVID-19 severity have not been fully studied and explained yet [2, 12, 25-28].

In the context of the aforementioned, the purpose of the present paper was to develop a narrative synthesis of contemporary studies on the correlation between the inflammatory biochemical indicators and hematometric markers with the severity, progression, prognosis and mortality of patients with COVID-19.

The publications were selected from the PubMed, Hinari, SpringerLink, and Google Search databases using the keywords: "COVID-19", "SARS-CoV-2", "C-reactive protein", "procalcitonin", "white blood cells", "lymphocytes", "neutrophils", "neutrophil-lymphocyte ratio", "platelets", "biomarkers", "severity prediction", which were used in various combinations to exploit the search results.

For an extended selection of bibliographic sources, the following filters were used: full-text articles, articles in English, articles published in 2020-2022. After processing the identified information and according to the search criteria, 724 full-text articles were selected. After excluding records not related to the purpose of the study, reviewing abstracts and full-text articles, 89 eligible original articles were selected with a variety of study designs, including editorials, descriptive synthesized articles, systematic and meta-analyses, and cohort studies that contained data on laboratory biomarkers found in patients with COVID-19, which have been qualified as possibly relevant for this synthesis.

In addition, bibliographic listings of the identified sources were searched to highlight additional relevant publications that were not found during the initial database search. After evaluating these sources, a total of 98 relevant publications were ultimately selected. The final bibliography of the present study included 98 articles, which were considered representative of the materials published on the topic of this narrative synthesis.

The information from the publications included in the bibliography was collected, classified, evaluated and synthesized, thus, highlighting the main aspects of the current view on the role of biochemical inflammatory indicators and hemocytometry markers in patients with COVID-19, their relationship and prediction of clinical outcomes, the severity and prognosis of SARS-CoV-2 infection.

In order to minimize the risk of bias within the present study, a thorough search of the databases was conducted to identify the maximum number of publications that were relevant to the study purpose. This present study also evaluated only those that met the criteria of validity, also used secure criteria for excluding articles from the study, and analyzed researches that showed both a positive result and those that do not highlight the benefit of determining inflammatory biochemical indicators and hemocytometry markers in COVID-19 patients.

If necessary, additional data sources were considered to clarify some concepts. Duplicate publications, articles that did not meet the purpose of the article and were not available for full review, peer review and commenting on articles, case series reports, articles with scarce or missing data on the values of the biomarkers under study, non-human studies and those on pediatric populations (<17 years) were excluded from the list of publications.

Results and discussion

The clinical spectrum of the SARS-CoV-2 infection varies greatly, which complicates diagnosis, prognosis and monitoring. Many patients with COVID-19 are asymptomatic or present mild symptoms. One subgroup of patients may initially develop severe disease form, while the non-severe form of the disease might worsen and evolve into a severe one followed by fulminant outcomes in other patients. On examination, subjective clinical symptoms can be more confidently interpreted using biological markers (biomarkers) that provide objective values during the COVID-19 development. The clinical course of the disease is unpredictable, which might suddenly develop, leading to critical clinical complications and even death [1, 2, 8, 12, 15, 16, 20, 29-32].

According to some scientists, systemic hyperinflammation or the "cytokine storm" plays a crucial role in the pathophysiology of SARS-CoV-2 infection [33, 34].

C-reactive protein (CRP). CRP is a non-specific indicator of systemic inflammation induced by various inflammatory mediators, occurring both in acute and chronic inflammation, as well as being an active regulator of the innate immunity. CRP is not only an excellent biomarker of inflammation, infection, and tissue damage, but is also directly involved in the pathological process: it contributes to the inflammatory response by releasing nitric oxide and producing cytokines. Thus, this protein plays a vital role in protecting against infections, preventing autoimmunity, regulating the inflammatory response [15, 20, 35-39] and is a useful marker for monitoring disease severity [20, 35-41].

CRP is typically absent in viral infections, while adaptive immunity is essential for eliminating the SARS-CoV-2 virus, thus, the macrophage activation syndrome may explain the high serum CRP level and how it contributes to disease progression in these patients [30]. Moreover, the strong inflammatory response that occurs in severe

COVID-19 can cause a significant increase in CRP levels [37, 42].

One of the earliest responses to a viral or bacterial infection is the activation of acute phase reagents, including CRP, ferritin, serum amyloid A, albumin, procalcitonin, erythrocyte sedimentation rate, and proinflammatory cytokines [15, 19, 37].

The main response during the CRP acute phase in COVID-19 could be predicted based on the well-known behaviour of this protein in general and, specifically, in severe viral respiratory infections. Initially, CRP values were found to correlate with the lung lesion diameter, thus characterizing the severity of COVID-19 (mild, moderate, severe, or critical), and predicting poor clinical outcomes, as reported in many, mostly small, cohort studies published worldwide [13, 15, 19, 22, 34, 43, 44]. Two retrospective cohort studies suggested that CRP had better results than other parameters in predicting adverse outcomes in COVID-19 patients [17, 43]. Furthermore, the serum level of CRP upon admission was identified as a moderate differentiation factor for disease severity [43]. Additionally, a large-scale study and several systematic literature reviews and meta-analyses that evaluated the main clinical outcomes of severe COVID-19 have demonstrated the clinical and biological prognostic significance of CRP as a marker of disease activity, prevalence, severity and mortality rate of COVID-19 [1, 2, 33, 45].

CRP activates the complement system, an important component of the innate immune system, induces production of pro-inflammatory cytokines, improves phagocytosis and induces apoptosis, which, together with the inflammatory tendency of COVID-19 progression, can lead to severe outcomes [20, 30, 40, 46, 47]. IL-6 is the most significant cytokine and the main trigger of the "cytokine storm", mainly inducing CRP and directly correlating with this protein levels in COVID-19 patients. However, the CRP activity as a potentially inducing factor of an inflammatory status, resulting in severe COVID-19 evolution, has not been widely assessed yet [15, 19, 20, 30, 35, 38, 39, 40, 47].

The clinical significance of CRP in patients with COVID-19 was demonstrated in two single-centre retrospective studies in China. The studies revealed that most of the patients with severe forms had a significantly higher CRP level, compared to those with the non-severe ones: 100 mg/L versus 9.65 mg/L, respectively ($p<0.001$) [1, 43] and 57.9 mg/L versus 33.2 mg/L, respectively ($p<0.001$) [12, 22]. Another retrospective study found higher CRP levels in patients with COVID-19 and severe CT findings compared with those with moderate to mild CT findings. People who died from COVID-19 had higher levels of CRP (85.3 mg/L) compared to survivors and patients who were discharged (53.5 mg/L) [1]. A study from Iran reported that patients with CRP levels >64.8 mg/dl were more likely to develop severe complications, with a sensitivity of 70.05% and a specificity of 70.59%, which was being associated with hospital death in COVID-19 patients [48]. Additionally, high CRP levels correlated with some common complications among COVID-19 patients (shock, ARDS, acute kidney failure, and acute cardiac failure) and may be a promising biomarker for assessing the mortality rates [29, 44, 46, 48]. CRP level ≥220 mg/dl, measured in the first week of hospitalization, increases the risk of death by 7.73 times and the risk of venous thromboembolism by 2.17 times, thus showing statistically significant results ($p<0.001$) [49]. In order to distinguish patients with COVID-19 in whom the condition may worsen during treatment, a cohort study has justified the target values for laboratory tests performed upon admission. For CRP, this value was 14.3 mg/L [16].

In the early stage of COVID-19, CRP levels positively correlate with the lung lesions diameter and the severity of the disease [21, 26]. A study conducted in the United States found that significantly elevated CRP levels correlated with a poor prognosis for patient survival. Thus, the CRP level turned out to be a simple, fast and economical tool for assessing the lesion severity, which contributes to the choice of therapeutic options for patients with COVID-19 [1, 41]. Additionally, two studies from Turkey and Iran concluded that the inflammatory parameters, including CRP, were associated with the severity of SARS-CoV-2 infection and can be used as important risk factors for disease progression and mortality prediction [1, 48].

Therefore, multiple studies have determined a sudden increase in CRP levels among patients with severe COVID-19, compared to individuals with non-severe forms (mild and moderate) [1, 32, 37, 33, 50, 51]. Analysis of pulmonary changes assessed by computed tomography revealed a positive association with CRP levels. Moreover, high CRP levels are determined prior to the onset of lung lesions, showing a predictive value for disease severity. The higher the initial values of CRP, the more severe the lung injury and the chances of developing ARDS become imminent [20, 36, 47]. In addition, an inverse correlation between high CRP levels and a decrease in partial pressure of arterial oxygen in the PaO2/FiO2 ratio, which indicates that CRP is also a predictor of acute respiratory failure [47].

Therefore, CRP levels can be the most efficient and sensitive biomarker in predicting the disease progression, as well as in early diagnosis and appropriate management of COVID-19 complications [1, 2, 37, 47]. Since changes in CRP levels occur prior to lung damage, this indicator can be used clinically to predict the prognosis and severity of COVID-19 before its progression and the onset of clinical symptoms [20].

A systematic literature review and meta-analysis based on 25 retrospective cohort studies with a total of 5350 participants found a significant association of CPR with an increased combined poor outcome (mortality, severe COVID-19, ARDS, and need for ICU hospitalization), in severe COVID-19 patients, with the need for ICU admission, but not with mortality alone. The value of CRP ≥10 mg/L has a sensitivity of 51%, specificity of 88% and a positive probability ratio of 4.1, being suggested as the cutoff value of CRP. Serum CRP can be used not

only as a prognostic marker but also for monitoring the improvement of COVID-19 condition [33].

Another systematic review and meta-analysis, conducted on 32 retrospective cohort studies that reflect data on 10491 confirmed COVID-19 patients, demonstrated an association between elevated CRP level (>10 mg/L) and combined poor outcome, which included ICU admission, oxygen saturation <90%, use of invasive mechanical ventilation, severe forms of the disease, and in-hospital mortality. Since the meta-analysis included studies from different geographical areas, the results provide global findings that can be generalized, while CRP can be used clinically as an early biomarker to identify individuals with increased risk, guide treatment and hospitalization needs, improve prognosis and reduce the mortality rate of COVID-19 patients [2].

In a systematic literature review, Yitbarek G. et al. found significantly higher mean CRP levels in patients with severe forms (81.28 mg/l) compared with patients with mild forms of COVID-19 (33.27 mg/l). /l). The same trend was found in all 15 retrospective cohort studies with a total of 15434 participants included in the review [1].

A systematic literature review and meta-analysis of 18 studies conducted on 3278 COVID-19 patients, including 732 patients with poor outcomes, and a retrospective cohort study of 456 patients with moderate COVID-19 form showed that high levels of CRP upon admission are associated with severe course of the disease, which are predictive of poor outcomes, such as hypoxia, need for ICU admission, need for mechanical ventilation, ARDS or death [17].

Another systematic literature review and meta-analysis of 16 eligible studies including 1896 survivors and 849 deceased patients with COVID-19 demonstrated a significant role of CPR in the outcome of SARS-CoV-2 infection. The deceased patients showed significantly higher concentrations of CRP compared to survivors. A significant association of CRP with mortality was found, while the persistence of high levels of this protein in individuals who died from COVID-19 suggests that CRP is a predictor for SARS-CoV-2 induced death.

The results of the other studies have also confirmed the correlation between CRP level, determined upon patient admission with the severity and mortality of SARS-CoV-2 infection, viz. the CRP level and length of stay were significantly higher in patients with severe forms compared to those with non-severe ones[16, 31, 37, 41, 47, 50, 52-54], the CRP level was higher among deceased patients compared to survivors [37, 43, 47, 48, 50, 53-55], as well as in patients hospitalized in ICU compared to those admitted to the COVID-19 unit [56]. A significant correlation between CRP concentrations and condition worsening in patients with non-severe forms of COVID-19 was observed [37]. A study from the UK demonstrated the significance of IL-6, being the most accurate predictor of death in patients with COVID-19, followed by CRP [1, 57].

Therefore, CRP levels can be an independent biomarker to determine the severity, unfavorable evolution, and mortality in COVID-19 patients, regardless of comorbidities, age, and gender. Trends in the dynamics of CRP values, compared to the initial level, combined with the evolution of clinical manifestations and the need for therapeutic interventions, provide more prognostic data that contribute to careful management of patients. For every unit increase in CPR levels, the probability of developing a severe form of COVID-19 increases by 5% [43, 47, 52, 54, 57, 58].

In conclusion, most studies have shown that SARS-CoV-2 infection is characterized by an excessive inflammatory response, especially in the severe form of the disease. CRP is an independent, accessible and easy-to-interpret biomarker and a key regulator of inflammatory processes. The level of this protein positively correlates and can be used to predict the severity, prognosis and mortality of COVID-19 patients, as well as to early predict the probability of disease progression in asymptomatic cases and in patients with mild infections. To predict the prognosis and severity of COVID-19, CRP can be clinically used before the disease exacerbation and onset of clinical symptoms. The determination of the evolution of CRP levels during COVID-19 patient's follow-up may be of great importance to clinicians in stratifying patients for being transferred to ICU, early detection of severe cases, need for invasive mechanical ventilation, favourable disease progression, followed by improved prognosis.

Procalcitonin (PCT) is traditionally used as a marker of systemic inflammation in the diagnosis of bacterial infections and the severity of sepsis, compared to viral infections, supporting clinical decision-making on the use of antibiotics. Its role in predicting the severity of COVID-19 disease is still being assessed [11, 18, 35, 42, 59-63].

In healthy individuals, the normal PCT level averages 0.033 ± 0.003 ng/ml and is not determined by the methods used in clinical laboratories. In severe infections (bacterial, parasitic and fungal), PCT levels may exceed 100 ng/mL. In viral infections and non-specific inflammatory processes, the PCT level is normal or slightly elevated [10, 63-65].

Bacterial endotoxins and/or cytokines (interleukin-6 and tumor necrosis factor alpha) are well-known triggers for PCT synthesis. High levels of these cytokines have been reported in severe COVID-19 infections. For this reason, PCT can also increase in a hyperinflammatory condition of COVID-19 patients in case a bacterial pathogen is absent [10, 11, 64].

An increase in PCT serum is often observed in hospitalized patients with moderate or severe COVID-19 [10, 11, 35]. PCT synthesis can be stimulated by elevated proinflammatory cytokines, including interleukin-6, interleukin-1β, and tumor necrosis factor alpha [10, 66]. These mediators are greatly involved in the "cytokine storm" that is typical of the transition from the viremia to the hyperinflammatory stage in COVID-19, being characterized by the onset of respiratory symptoms and interstitial lung infiltrates, as shown on chest imaging [18].

Currently, there are more evidence-based associations between elevated plasma PCT concentrations with adverse COVID-19 outcomes. PCT is a predictive biomarker and an

independent predictor of clinical and adverse outcomes in hospitalized patients with COVID-19, including moderate to severe and critical disease progression, need for ICU admission, need and duration of mechanical ventilation, and mortality rate [60, 64, 67, 68].

Patients with a baseline PCT level >0.1 ng/mL required significantly longer mechanical ventilation (averaging 5.6 days) than patients with a level ≤0.1 ng/mL (p=0.021), a level that can identify patients at risk for prolonged mechanical ventilation at admission. However, there was no significant difference in mortality at 28 days [69]. Two other retrospective studies found an association between PCT levels and the disease severity, but no correlations were found with in-hospital mortality, total length of hospital stay, or ICU length of stay. These results refute several previous studies that found that PCT levels correlated with ventilator duration and mortality [17, 70].

A series of systematic literature reviews, meta-analyses, cross-sectional and observational retrospective studies have demonstrated an association of elevated PCT levels (> 0.5 ng/mL) with COVID-19 disease severity, rapid disease progression, risk of sepsis, admission to the intensive care unit, use of invasive mechanical ventilation or even death. Patients with severe forms of COVID-19 showed a statistically significantly higher increase in PCT compared to patients with non-severe forms [5, 7, 10, 11, 13, 15, 17, 19, 22, 26, 42, 63]. Patients with non-surviving COVID-19 had higher initial PCT levels upon ICU admission compared to surviving patients [18, 65].

The results of a study showed that the mean serum PCT level was over 4 times higher in patients with severe COVID-19 compared to patients with moderate forms of the disease, and over 8 times higher in critically ill patients compared to patients with moderate forms of the condition. Among the discharged patients, both normal and abnormal PCT levels declined during recovery. However, in cases of death, serum PCT levels increased as the disease exacerbated. Thus, PCT may be an indicator of COVID-19 severity that may help determine the severity of patients infected with SARS-CoV-2, and PCT measurements during patient's follow up can be useful in predicting prognosis [68].

Two meta-analyses, which included 52 studies conducted on 6320 and 15296 patients, respectively, have shown a significant statistical association between PCT and the severity of COVID-19. Patients with a high PCT level had a greater chance of developing a severe form of the disease [24, 71]. Another meta-analysis, conducted on 49 studies with a total of 20211 COVID-19 patients, showed an association between 18 factors with a combined adverse outcome, which included death, severe COVID-19 forms, need for ICU admission and/or the need for mechanical ventilation. One of these factors was a high level of PCT that scored 4.8. However, elevated PCT has not been associated with patient's mortality [72].

Any significant increase in PCT (>0.5 ng/mL) is indicative of bacterial co-infection or the development of severe COVID-19 and a more complex clinical picture, whereas a slight increase in PCT (<0.5 ng/mL) is an important indicator for distinguishing between positive and negative patients with SARS-CoV-2 [10]. A recent meta-analysis showed that 63.7% of patients had severe COVID-19 among patients with elevated PCT values, compared with 27.0% of patients with negative PCT [11].

Thus, PCT is a promising prognostic biomarker of COVID-19 progression [71]. However, some studies have shown that the association between elevated PCT concentrations in COVID-19 patients with respiratory failure and mortality may be independent of bacterial co-infection [60]. Therefore, although some authors assume that this positive association reflects the presence of bacterial co-infection, currently there is no adequate evidence to support this hypothesis [11, 60].

A high PCT level at admission may indicate a more severe course of COVID-19 infection with adverse outcomes [11, 64, 70]. A meta-analysis that included 4 studies involving 1418 patients showed that elevated PCT levels increase the risk of severe COVID-19 by about 5 times [10, 68, 73, 74], whereas another meta-analysis conducted on 12 studies that included 2794 patients, of which 596 (21.33%) were patients with severe COVID-19, found that elevated PCT levels were associated with severe SARS-CoV-2 infection [66].

Moreover, a meta-analysis of 25 studies involving 5350 patients with COVID-19 found that elevated PCT levels were associated with an increased risk of poor combined outcomes, including mortality, severe acute respiratory distress syndrome (SDRA), need for intensive care unit admission, and disease severity. The subgroup analysis showed that elevated PCT was associated with an increased risk of mortality and severe COVID-19. A PCT level ≥0.5 ng/mL had a sensitivity of 88% and a specificity of 68% for poor combined outcomes in COVID-19 [33].

Another meta-analysis, which included 32 studies with 10491 COVID-19 patients under study confirmed that elevated PCT levels (>0.5 ng/mL) are associated with the COVID-19 severity and might be used in predicting disease exacerbation. Furthermore, high PCT level may increase the risk of poor combined outcomes by 6 times, which included ICU admission, oxygen saturation <90%, invasive mechanical ventilation, severe forms of the disease, and in-hospital mortality. The meta-analysis included studies from different geographical areas, thus, the results provide global conclusions that can be generalized, and PCT can be used in clinical practice as an early biomarker to improve management and prognosis, as well as reduce the mortality rate of patients with COVID-19 [2].

PCT is significantly associated with both mortality and probability of ICU admission of patients with COVID-19. As PCT levels increase, so does mortality. The obtained data suggest that PCT shows the severity of pneumonia during SARS-CoV-2 infection, which makes it possible to identify patients requiring ICU admission. These results contribute to a growing number of evidences for the usefulness of PCT in the context of COVID-19 infection to guide ICU management and proper resource allocation [74].

As PCT levels increase among hospitalized COVID-19 patients, there is a significant trend (p<0.0001) of increased disease severity and lung parenchyma injury, determined by imaging and laboratory findings [26, 67].

High PCT levels in COVID-19 patients are associated with clinical, imaging and laboratory characteristics of disease severity and respiratory failure requiring a prolonged invasive mechanical ventilation, longer ventilation duration and increased risk of in-hospital death [60], although in some studies, an increase in PCT was strongly associated with hospital mortality only in older patients (>75 years) [67].

Thus, PCT may be an indicator of disease severity, may facilitate timely intervention, and should be used as a marker for risk assessment and prognosis in patients with COVID-19. Routine determination of PCT within ICU contributes to identifying COVID-19 patients at risk of developing early ARDS and clinical decision-making, while repeated PCT findings during the patients' follow-up may be useful in predicting prognosis, improving survival rate, and optimizing healthcare resources allocation, which may be quite limited in some countries.

Leukocytes. Leucocytes were generally normal or low upon the admission of COVID-19 patients [75]. As the disease progressed, a significant increase in the number of leukocytes was revealed, which is more common in severe COVID-19 compared to non-severe cases [5, 15, 18, 19, 22, 26, 75-78]. The leukocyte count was higher in the group of critically ill patients, compared to patients with severe or non-severe forms of the disease [54, 75]. Furthermore, the number of white blood cells (WBC) was significantly and directly associated with the severity of COVID-19, whereas the leucocytosis (>10×109/L), determined upon the admission of COVID-19 patients, caused a 3-fold higher risk of exacerbation and evolution to a severe form of the disease [15, 54, 75].

These results are supported by several systematic literature reviews and meta-analyses. A meta-analysis based on 52 studies that included 6320 patients with COVID-19 showed that patients with leukocytosis were more likely to develop a severe form, being admitted to the ICU [24]. Another meta-analysis conducted on 21 studies included 3377 patients with COVID-19 and showed a significant increase in white blood cell count among patients with severe and fatal forms of the disease, compared with patients with non-severe forms and survivors [10, 79, 80]. An optimal cutoff value (3.3 x 10^9/L) for the number of leukocytes for differentiating severe from non-severe forms of COVID-19 was also determined [77].

However, some studies have found a decrease in WBC count in both mild and severe cases [75]. A meta-analysis of 22 studies that included 3396 patients with COVID-19 also did not reveal significant changes in the number of leukocytes in patients with severe and non-severe forms of the disease upon ICU admission [7].

Thus, COVID-19 patients show normal or low WBC count upon admission that increases simultaneously with the disease progression. Leukocytosis is associated with an elevated number of neutrophils, tendencies to reduce lymphocytes, monocytes and eosinophils, which means clinical worsening and an increased risk of poor outcomes. However, in some severe cases of COVID-19, leukocytosis may be caused by viral/bacterial co-infections, corticosteroid administration, or *immune response variability.*

Neutrophils were mostly normal in non-severe COVID-19 patients, but increased in severe infections [7, 22]. A systematic literature review and meta-analysis of 22 studies involving 3396 patients with COVID-19 found a significant increase in neutrophil counts in patients with severe disease compared to patients with non-severe disease forms [7].

The possibility that neutrophilia is a predictor of disease severity and poor prognosis has been supported by several studies [15, 19, 75, 81]. Overall, neutrophil counts were statistically significantly higher in non-survivors than in survivors [18, 19, 75, 81] and in patients with severe cases compared with patients with non-severe forms of COVID-19 [15, 19, 75].

A meta-analysis of 52 studies involving 6320 patients with COVID-19 found that patients with neutrophilia were more likely to develop severe disease phenotype, being admitted to the intensive care unit, and were more likely to die. The prognostic neutrophil cutoff value for identifying patients at high risk of severe COVID-19 was ≥3.74×109/L [24].

In contrast to studies reporting neutrophilia, other smaller studies stated opposite conclusions. The latter did not find neutrophilia but a significant decrease in granulocytes (eosinophils, basophils, and neutrophils) in patients with severe COVID-19 compared to non-severe forms, normal and even low neutrophil counts in COVID-19 patients compared to healthy control group, though, when comparing the disease severity, the leukocyte count was much higher in patients with severe forms of the disease [75].

Thus, the number of neutrophils in blood is normal in patients with non-severe forms of COVID-19 and increases along with severe infections. Neutrophilia was significantly associated with the risk of disease progression to a severe phenotype, as well as the risk of ICU admission, and even death.

Lymphocytes. All studies reported lymphocytopenia, which is the most common hematologic abnormality and correlates with COVID-19 severity. In patients with a severe form of the disease, the number of lymphocytes is significantly reduced compared to patients with non-severe forms [5, 7, 18, 22, 26, 75, 76, 78, 82, 83]. Large-scale studies have shown that 83.2% of hospitalized COVID-19 patients had lymphocytopenia upon admission [75], which was more and less prominent in severe and critical cases (80–85.7%) [10, 27, 63, 84] compared to non-severe cases (25-44.4%) [10, 14, 27, 84].

These results were confirmed by three meta-analyses. A meta-analysis of 32 studies involving 10491 COVID-19 patients showed that lymphocytopenia is associated with a significantly higher risk of poor outcomes in hospitalized

COVID-19 patients [2]. Another meta-analysis conducted on 21 studies involving 3377 COVID-19 patients found a significant decrease in the number of lymphocytes among patients with severe and fatal forms of the disease compared to non-severe cases and survivors [10, 79]. A systematic literature review and meta-analysis performed on 22 studies involving 3396 COVID-19 patients showed a significant decrease in the number of lymphocytes in patients with severe disease compared with patients with non-severe forms [11].

The decrease in the number of lymphocytes upon admission was the most important and sensitive marker in predicting the severity, progression and outcome in patients with COVID-19 [15, 19, 75, 83]. More severe lymphocytopenia was predominantly present in non-survivors compared to survivors [18, 19, 48, 75, 82].

Thus, during the incubation and early stage of COVID-19 disease, the number of lymphocytes in peripheral blood is normal or slightly reduced. Lymphocytopenia, regardless of other indicators, comorbidities, age and gender, correlates with the COVID-19 severity and is a reliable indicator of early infection with SARS-CoV-2 and poor prognosis, as well as contributes to the assessment of disease progression. An association has been demonstrated between lymphopenia and the need for ICU care, the development of ARDS, and increased risk of death.

The neutrophil-lymphocyte ratio (NLR) constantly increases in patients with severe COVID-19, compared to patients with non-severe forms. In addition, the prognostic value of NLR as an independent predictor of severe forms and progression of SARS-CoV-2 infection has also been demonstrated [5, 15, 27, 75-78].

Several studies have highlighted a significant association of NLR with COVID-19 severity [10, 77, 82, 85]. A higher NLR upon admission was an independent predictor for the development of severe COVID-19, for poor clinical outcome among COVID-19 patients [4, 21, 75, 77, 82, 85] and for the lethal outcome due to COVID-19 [9, 76, 85, 86]. According to some study results, the NLR value equal to 2.973 upon admission, with a specificity of 66.8% and a sensitivity of 75.8%, may predict disease progression during hospitalization [10, 87], NLR value of 3.2-4.795, with a sensitivity of 56.3-88.3% and a specificity of 63.6-83.7%, may predict a severe COVID-19 form [5, 77, 88], and NLR value > 6, with a sensitivity of 86.7% and a specificity of 84.4%, predicts death due to COVID-19 ($p < 0.001$) [88]. NLR, determined upon admission, was independently associated with death in patients with severe COVID-19, namely, the risk of death increased by 5.7% for each unit increase in NLR [89]. Therefore, the NLR value can indicate the COVID-19 severity and outcomes [5, 10, 77, 87, 88].

Small studies have reported high NLR in severe cases of COVID-19 [22, 75]. A study including a cohort of 452 patients with COVID-19 found that patients with severe infection (286 patients) had a statistically significantly higher NLR compared to patients with non-severe forms (5.5 and 3.2; $p<0.001$) [22].

A series of studies have suggested that an elevated NLR level is largely associated with the severity of COVID-19, being an independent biomarker of poor clinical outcomes, viz. the disease progression to severe, critical and even fatal ones [17, 19, 77]. Multivariate analysis showed that with an increase in NLR per unit, the risk of in-hospital death increases by 8%, whereas the deceased patients had a NLR ≥10.8 [86].

Two systematic literature reviews and meta-analyses conducted on 6 and 22 studies involving 828 and 3396 patients with COVID-19, respectively, found a significant increase in NLR values in patients with severe forms compared with patients with non-severe forms of the disease [10, 11, 90]. Another more recent and larger meta-analysis that included 64 studies involving 16205 COVID-19 patients found that NLR upon admission predicted both severity and mortality, and NLR >6.5 was associated with significantly higher mortality rates. The authors concluded that NLR is a consistent biomarker for predicting the disease severity (with a sensitivity of 80.2% and specificity of 75.8%) and mortality (with a sensitivity 78.8% and specificity of 73.0%) of COVID-19, regardless of age, gender, or comorbidities [91].

To improve the stratification and management of patients with COVID-19, a predictive model based on NLR and age was developed. The incidence of severe SARS-CoV-2 infection was only 9.1% in patients aged ≥50 years and NLR <3.13, while 50% of patients aged ≥50 years and NLR ≥3.13 developed a severe COVID-19 [75]. Around 94.5% of patients who died from COVID-19 complications had a NLR >5 [75, 81]. Due to the confirmed consistency and significance, high NLR can be used as an admission-screening tool to identify patients with increased risk of COVID-19 [75].

According to the results of a systematic literature review and a meta-analysis that evaluated 29 studies involving 4911 patients, NLR may be a better biomarker of systemic inflammation and COVID-19 severity than neutrophil or lymphocyte counts, analysed separately [15].

Therefore, elevated NLR results from an increase in the number of neutrophils and a decrease in the number of lymphocytes, which can be quickly calculated based on a routine blood test upon the patient admission. For patients with COVID-19, NLR has been shown to be an independent risk factor for severe forms of the disease, viz. there is a strong relationship between increasing NLR levels and COVID-19 severity. NLR is an early inflammatory marker that reveals severe and critical infection with SARS-CoV-2, as well as being an independent risk factor of in-hospital mortality for COVID-19 patients.

The NLR assessment can help identify individuals at high risk of contracting COVID-19, early detection, as well as in treatment of severe pneumonia in COVID-19 patients. This marker is very important, especially in areas where diagnostic tests are limited, which often creates difficulties in diagnosing SARS-CoV-2 infection. However, further research is needed to confirm these findings, to

compare the predictive ability, as well as to determine the change in NLR depending on the treatment used.

Platelets. Platelet counts upon admission tended to be lower in severe cases of COVID-19 compared to non-severe cases [5, 7, 18, 19, 75], as well as in non-survivors compared to survivors [10, 18, 19, 28, 92].

Low platelet count has been identified as a prognostic factor and an indicator of the disease severity and clinical worsening during hospitalization [75]. Thrombocytopenia has been associated with an increased risk of severe disease, the need for ICU hospitalization, and mortality in patients with COVID-19 [10, 19, 28, 92]. Terpos et al. showed more frequent thrombocytopenia in patients with severe forms of COVID-19 (57.7%) compared to patients with non-severe forms (31.6%) [14]. Zhang et al. reported a platelet count <100×109/L in the last 24 hours before death in 63.2% of patients infected with SARS-CoV-2 [75, 81]. A large study conducted on 1476 COVID-19 patients, including 1238 (83.9%) survivors and 238 (16.1%) non-survivors, found thrombocytopenia in 306 (20.7%) cases, with a statistically significant increase in patients who died compared to survivors (72.7% vs 10.7%, p<0.001). The authors found a significant relationship between platelet count and COVID-19 mortality, with lower platelet counts associated with higher mortality. In patients with platelet counts of 0-50x109/L, 50-100x109/L, 100-150x109/L, and >150x109/L, the in-hospital mortality rate was 92.1%, 61.2%, 17.5%, and 4.7%, respectively (p<0.001) [28].

The role of thrombocytopenia as a clinical indicator of exacerbation and prognosis of patients with SARS-CoV-2 during hospitalization, as well as a predictor of severity and mortality of COVID-19 patients has been confirmed by systematic review and meta-analysis studies. A systematic literature review and meta-analysis of 22 studies, conducted on 3396 COVID-19 patients, found a significant drop in the number of platelets in patients with severe forms of the disease, compared to patients with the non-severe forms [7]. A meta-analysis that included 21 studies involving 3377 COVID-19 patients demonstrated a significant reduction in the number of platelets among patients with severe and fatal forms of the disease compared to non-severe forms and survivors [10, 79]. Another meta-analysis evaluated 9 studies involving 1779 COVID-19 patients, including 399 (22.4%) with severe forms, which suggested that thrombocytopenia is significantly associated with COVID-19 severity. A greater decrease in platelet counts was observed in deceased patients [14, 92].

However, some studies have not found significant differences in platelet counts between patients with severe and non-severe forms of COVID-19 [76].

Thus, patients with COVID-19 typically have normal or low platelet counts upon admission, though dynamic changes might occur during hospitalization. Several systematic reviews, meta-analyses, and studies have shown that thrombocytopenia is a predictor of severity and mortality in patients with COVID-19. Thrombocytopenia has been associated with an increased risk of over 5 times for severe forms of COVID-19. Platelet count monitoring may be useful as a clinical indicator of deterioration and prognosis in patients with SARS-CoV-2 during hospitalization.

In conclusion, the results of the present summary article show that there is clear evidence for an association between inflammatory and hematological laboratory biomarkers and the severity of COVID-19. These marker levels exhibit the intensity of the cytokine-mediated hyperinflammatory response and are strongly associated with poor outcome of SARS-CoV-2 infection. The greater the change in indicators, the greater the incidence of severe COVID-19 [58, 76]. They can be used as an adjuvant in clinical practice to guide treatment and hospitalization needs, to improve prognosis and reduce mortality, as well as to manage health care resources appropriately. The combined analysis of prognostic biomarkers contributes to a more accurate identification of the flare-up risks of severe COVID-19 resulting into unfavourable prognosis in patients with mild or moderate forms of the disease [2, 51].

Nevertheless, the interpretation of some study results present in this summary paper is limited due to the predominance of retrospective single-centre, small-sized sample studies due to the lack of consistency in determining the severity of the disease, lack of an accurate chronology of laboratory sample collection, lack of serial measurements of samples, as well as the termination of some studies without reporting the final results, since prompt data publication is required during a pandemic situation [19]. An assessment of the accuracy of these biomarkers needs to be determined in more relevant multi-centre studies with more precise designs, more in-depth performance, and larger sample sizes [2].

Conclusions

1. Inflammatory biochemical markers and hemocytometry markers are feasible, easily interpretable, and widely accessible biomarkers in most healthcare centres, as well as favourable for being used in the management of COVID-19 patients.

2. C-reactive protein correlates positively and can be used to predict the disease severity, prognosis and mortality in addition to vital signs' monitoring, supportive care, oxygen therapy, ventilation and circulation support in patients with SARS-CoV-2 infection.

3. In order to guide treatment and monitor patients, predict the prognosis and COVID-19 severity, C-reactive protein can be used clinically even prior to disease progression and the onset of clinical symptoms. Serial determination of C-reactive protein levels during the COVID-19 patients' follow-up has become an important diagnostic algorithm for admitting patients to the intensive care unit, early detection of severe cases, as well as for early implementation of invasive or non-invasive ventilation techniques, disease progression and outcome assessment.

4. Procalcitonin is a promising predictive biomarker for COVID-19 disease progression, whereas the association between elevated procalcitonin concentrations in COVID-19 patients with respiratory failure and mortality shows independence of bacterial co-infection.

5. Procalcitonin may be an indicator of disease severity and may facilitate timely intervention. It should be used as a marker for risk assessment and prognosis in COVID-19 patients. Routine procalcitonin testing within the intensive care unit may identify patients with COVID-19 who are at risk of developing early acute respiratory distress syndrome and may facilitate clinical decision-making and serial measurements of procalcitonin that are useful in predicting prognosis and improving patient survival, as well as in optimizing medical resources allocation.

6. Leukocytosis, neutrophilia, lymphocytopenia, neutrophil/lymphocyte ratio, and thrombocytopenia have been identified as independent factors for poor clinical outcome in patients with COVID-19 and can be useful in predicting disease progression, need for ICU admission, and mortality rate.

7. The estimation of laboratory hematological parameters upon admission, used in differentiating severe cases from non-severe ones and high-risk cases from those with low mortality risk, allows raising awareness, proper follow-up and timely treatment of patients with COVID-19, as well as early improvement of their clinical condition.

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NC conducted literature review, and wrote the first version of the manuscript; RB conceptualized and designed the idea; OA and SS revised critically the manuscript and completed the final text; IC and OG wrote the manuscript; RB and VM conducted literature review. All the authors read and approved the final version of the manuscript.

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