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Inflammatory syndrome in SARS-CoV-2 infection

PHD THESIS ABSTRACT

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Introduction

In the context of the COVID-19 pandemic, the General Secretary of the United Nations emphasized the need for a common fight, shortly before the World Health Organization declared the beginning of the COVID-19 pandemic [1]. This prompted unprecedented global measures such as isolation and travel restrictions, but also joint efforts to develop effective vaccines [2]. Similar to other countries, Romania faced an increase in the number of infections and implemented strict measures, which had a negative impact on daily life and the economy [3].

The doctoral study focused on analyzing the pathophysiology of COVID-19, identifying predictive markers and evaluating hematological indices such as NLR and RTL to predict the severity of the disease [4]. The research proposes to investigate biomarkers and interleukins, genetic and environmental factors, and develop integrated predictive models to personalize treatment and improve the management of patients with severe forms of COVID-19 [5]. Future studies will explore their influences in long-COVID syndrome and personalized therapeutic strategies [6].

Chapter 1- SARS-CoV-2 infection, host immune response and inflammatory syndrome:

***General information*:** In this subchapter of the general part, I have addressed notions from the literature on the epidemiology of SARS-CoV-2 infection, virus structure, transmission pathways and notions about viral variants (alpha, beta, gamma, delta omicron and new strains also recombinant variants [7, 8, 9, 10, 11, 12, 13]. I have also included in this chapter information on COVID-19 prophylaxis, related to currently available vaccines [14, 15, 16].

Pathophysiology of SARS-CoV-2 infection: this subchapter describes how SARS-CoV-2 virus manages to enter the host cell and how it replicates. The attachment of SARS-CoV-2 depends on the presence of ACE2, heparan sulfate and neuropilin-1 on the host cell surface [17]. Moreover, I have also detailed the mechanisms of fusion, which involve first conformational changes of protein S and subsequent virus penetration into the host cell [18, 19, 20, 21, 22]

Extremely important is the host immune response, which involves first the activation of the innate immune system and subsequently the activation of the adaptive immune system, via the PRR [23]. Thus, the process of IFN-alpha synthesis, macrophage activation and secretion of various cytokines that sustain the actions of the immune response as well as antibody synthesis will be initiated [24, 25, 26].

Excessive activation of the inflammatory syndrome in SARS-CoV-2 infection is the prerogative of the cytokine storm, i.e. the imbalance between the secretion of pro- and anti-inflammatory cytokines that can produce significant injury, sustaining the immune system activity in an exaggerated manner, which can lead to ARDS, multiple organ failure or death [27, 28, 29].

Endothelial dysfunction and procoagulant status-In this subchapter we described the mechanisms by which this entity, also known as endothelitis, influences patient outcome and prognosis [30, 31, 32, 33]. Also, prothrombotic mechanisms are extremely important events that increase the severity of the disease forms [34, 35, 36, 37].

Chapter 2- Assessment of SARS-CoV-2 infection and inflammatory markers in clinical practice

The subchapter titled "Diagnosis of SARS-CoV-2 infection" includes data on the diagnosis of SARS-CoV-2 infection and inflammatory markers.

Clinical criteria- Data are detailed regarding the clinical picture in COVID-19, represented by fever and dry cough (the most encountered symptoms), considered to be also the most important in the clinical diagnosis of the disease forms [38, 39, 40, 411].

Non-specific laboratory diagnosis- depending on the form of the disease, patients present with various non-specific changes in blood tests (lymphopenia, leukocytosis with neutrophilia - in severe cases of the disease, thrombocytopenia, coagulation disorders [42].

Specific (etiologic) laboratory diagnosis - the "gold standard" for the specific diagnosis of SARS-CoV-2 infection is the polymerase chain reaction PCR technique [43]. Used especially during the pandemic period, antigen-rapid tests are no longer recommended to be used in clinical practice at present due to false-negative results [44, 45].

Complementary paraclinical examinations involve the use of radiography and lung CT scans, which have some disadvantages because they cannot identify specific COVID-19 lesions. Instead, they provide valuable information regarding the form of the disease and the degree of lung involvement [46, 47].

The forms of disease (moderate, mild, severe) presuppose the existence of certain clinical and imaging changes that, in conjunction, may place the patient in a particular risk group [48].

Cytokines are a key element in the immune response and their overproduction leads to a hyperactivation of the immune system with disastrous consequences for tissues and organs, known in the literature as the 'cytokine storm' [49].

Acute phase reactants, such as C-reactive protein, procalcitonin and ferritin, play a significant role in monitoring and assessing the severity of COVID-19 infection. They are characterized by elevated serum levels [50, 51].

Hematologic indices such as neutrophil/lymphocyte ratio is another useful marker in the evaluation of severe and critical forms of COVID-19. In this context, the NLR (neutrophil/lymphocyte ratio) is proving to be a valuable tool for predicting the course of infections and the risk of developing severe forms of the disease, with applications also in the diagnosis of other infections such as pneumonia or bacteremia [52, 53, 53, 55].

Studies have shown that severe and moderate forms of disease are associated with increased levels of CK, CKMB, troponin and LDH, indicating the presence of cardiac involvement. [56, 57, 58].

Chapter 3- Working hypothesis and general objectives

Research hypothesis:

1.The value of some hematologic indices (such as neutrophil/lymphocyte-NLR, platelet/lymphocyte-LRTI ratio) correlates with the severity and course of COVID-19.

2. The serum levels of some biomarkers (creatine kinase, CK-MB, myoglobin, troponin I) correlate with the duration of hospitalization and with the occurrence of complications during hospitalization, especially cardiovascular complications.

3. Elevated serum levels of interleukins correlate with disease severity.

4. Genetic and environmental factors such as gender differences, body mass index (BMI) and co-medications influence cytokine levels.

5. Development of predictive models that can predict the clinical course of patients, including risks of hypoxemic respiratory failure, development of complications during hospitalization and length of hospitalization.

6. The prediction models developed will allow early identification of patients at increased risk of severe COVID-19.

The research objectives: were outlined in the 3 articles published in the PhD research [59, 60, 61].

1. To evaluate the correlations between hematologic indices - NLR and RTL - and the severity and evolution of COVID-19.

2. Investigation of possible correlations between increased levels of cardiac biomarkers to determine their role in the occurrence of cardiovascular complications.

3. Studying correlations between increased serum levels of IL-6 and IL-1 with COVID-19 severity.

4. Investigate the impact of genetic and environmental factors (gender differences, BMI, co-medications) on the immune response of COVID-19 patients.

5. Development of an integrated predictive model to predict the risks of respiratory failure, cardiovascular complications and duration of hospitalization- is geared towards the development of a predictive model that is essential for the practical applicability of the research.

6. Formulate clinical recommendations based on the data obtained from the development of predictive models.

Chapter 4- General research methodology

To conduct the study, we obtained the necessary approvals from the Ethics Commission of the National Institute of Infectious Diseases "Prof.. Dr. Matei Balș" in Bucharest, following the detailed presentation of the research methodology, protocol and publication intention.

We also requested access to the patients' observation records, and the approval was issued by the hospital management and the Legal Department. The studies conducted were observational, retrospective and the data collected were statistically analyzed using SPSS software.

Chapter 5- Importance of neutrophil/lymphocyte and platelet/lymphocyte ratio in predicting critical outcomes in patients with COVID-19

The immune system plays an essential role in combating SARS-CoV-2 infection. In the early stages of the disease, the innate immune response is activated, but as the disease progresses, the adaptive immune response is also activated, with activation of T and B lymphocytes. The problem arises when this immune response is out of balance and the

'cytokine storm' is unleashed, with devastating effects on the body. These changes in the immune system correlate with increased levels of neutrophils and decreased lymphocytes in severe cases [62, 63, 64].

Neutrophil/lymphocyte and platelet/lymphocyte ratios were investigated as potential biomarkers able to predict disease progression [65, 66].

The main aim of the study was to investigate whether there is any association between increased levels of these reports and disease severity, need for hospitalization or admission to ICU and to assess the predictive power of these reports on disease progression, complications or days of hospitalization in COVID-19 patients in Romania.

We conducted a retrospective, observational study at the National Institute of Infectious Diseases "Prof.. Dr. Matei Balș" in Bucharest, Romania, between December 31, 2020 and October 8, 2021. The study included 536 patients diagnosed with COVID-19. P

The prediction model created showed that a higher NLR and RTL significantly increased the risk of developing bacterial superinfection, suggesting that these biomarkers may be useful tools for risk stratification in patients with COVID-19.Although C-reactive protein (CRP) is a well-known marker in clinical practice, the study emphasized that NLR and RTL offer additional advantages in assessing the severity of COVID-19 severity, particularly in predicting respiratory failure and complications.

The results of the study highlight the predictive value of a combined model including NLR, RTL and CRP in predicting the outcome of patients hospitalized with COVID-19, correlating elevated levels of these biomarkers with critical clinical events such as acute respiratory failure, development of complications and the need for antibiotics.

The study demonstrates that these two reports could be useful tools for identifying patients at high risk of severe forms of the disease and monitoring their disease progression, and future research could explore the use of these biomarkers in early treatment adjustment and assessment of therapeutic effectiveness.

Chapter 6- New insights into serum CKMB, myoglobin and troponin I levels as predictors of COVID-19 severity and length of hospitalization

The effects of SARS-CoV-2 on the cardiovascular system are currently intensively studied, with a significant impact on morbidity and mortality. The mechanisms by which SARS-CoV-2 affects the heart include both the direct effects of the virus and complications developed in patients with pre-existing conditions, such as systemic inflammatory response, endothelial dysfunction and hypercoagulability [67, 68, 69].

Our study identified statistically significant correlations between elevated levels of cardiac biomarkers and longer lengths of hospitalization, acute respiratory failure, and the development of complications during hospitalization.

We conducted a retrospective observational study on 472 patients hospitalized at the National Institute of Infectious Diseases "Prof.. Dr. Matei Balș" in Bucharest.

Our study identified a statistically significant association between elevated levels of cardiac biomarkers and unfavorable outcomes in patients hospitalized with COVID-19. Biomarkers such as CKMB, myoglobin and troponin I were correlated with longer hospitalization, acute respiratory failure and cardiac complications. These markers are valuable indicators of myocardial injury and can help assess the cardiovascular risk of patients, providing essential information for clinical decision-making.

The predictive models developed in our study demonstrated a good ability to identify patients at increased risk of acute respiratory failure and complications. These results emphasize the importance of careful monitoring of patients with elevated levels of cardiac biomarkers, who may benefit from early interventions to prevent deterioration of their condition.

Chapter 7- Role of IL-6 and IL-1 in COVID-19 progression: impact of gender differences, BMI variability and co-medications

COVID-19 elicits an abnormal immune response, leading to a cytokine storm" (CRS), responsible for severe hyperinflammation and negative disease prognosis. Comorbidities such as obesity and diabetes can worsen the course of the disease. Studies suggest that treatments targeting the NLRP3 inflammasome and IL-1β, such as anakinra, may improve survival and shorten hospitalization. Elevated IL-6 levels are also associated with disease severity and

may predict clinical outcomes. Genetic and environmental factors influence immune response and disease severity, and glucocorticoids may improve survival in severe forms [70, 71, 72].

We conducted a retrospective study on patients hospitalized at the National Institute of Infectious Diseases Prof. Prof. Prof. Prof. Prof. Prof. Prof. Dr. Matei Balș in Bucharest, Romania.

IL-1 is an essential cytokine in the immune system with significant roles in both innate and adaptive immunity. Some studies suggest that elevated IL-1 levels are present in patients with severe forms of COVID-19, but others have not demonstrated a significant correlation between its levels and disease severity. Age, comorbidities and hormonal sex differences may influence these results [73, 74, 75, 76].

Elevated IL-6 levels are associated with severe forms of COVID-19, including ARDS, and may damage alveolar and endothelial structure, contributing to hypoxia. Studies suggest that IL-6 may be a better predictor of disease severity than IL-1, with significantly higher values in severe cases [77, 78].

In our study, IL-6 was more strongly associated with disease severity than IL-1, being a more reliable predictor for COVID-19 progression, especially in severe forms. Gender differences, influenced by estrogen in women, and decreased immune function in the elderly may explain the variability in immune response and disease severity. Higher levels of IL-6 were related to lower BMI, whereas IL-1 correlated significantly only in men. IL-1 was also associated with cough and IL-6 with abdominal pain in men and myalgias in women.

Chapter 8- Conclusions and personal contributions

The thesis is structured in two parts: a general part and a personal contribution part. The general part includes a literature review on SARS-CoV-2 infection. It details the mechanisms by which the virus enters the host cell, the pathophysiologic reactions such as cytokine storm and endothelial dysfunction, which lead to severe complications and negative prognosis. Diagnostic methods and the importance of inflammatory biomarkers in assessing disease severity and prognosis are also described.

The personal contributions part presents the research performed, including relevant studies published in scientific articles. Studies focus on the identification of biomarkers useful in the diagnosis and prognosis of COVID-19, such as neutrophil/lymphocyte and platelet/lymphocyte ratio, which may predict the risk of complications and the need for admission to ICU. Another study explores cardiac biomarkers (CKMB, myoglobin and

troponin I), demonstrating their usefulness in predicting disease severity and length of hospitalization.

The thesis also addresses aspects related to the variability of the immune response and factors such as patients' age, gender and comorbidities. In this context, the interleukins IL-6 and IL-1 play an important role in determining disease severity. The research results suggest the need for personalized treatments and pave the way for further research, particularly in the field of long-COVID syndrome, which affects patients in the long term.

Strengths of the research include conducting the studies in a reference center in the field and collaboration with a multidisciplinary team. The large cohort size (536 patients) and the use of cost-effective predictive models allow an efficient assessment of risks and complications. The research has also been presented at international scientific events, contributing to the dissemination of knowledge. An important point of the research is the applicability of the results in clinical practice.

In terms of limitations, the research is based on a retrospective study, which may introduce errors, but the analysis was carried out following rigorous protocols and a detailed statistical evaluation. The changing epidemiologic context influenced the initial prospective studies, but the retrospective approach was adjusted to provide relevant data on pathophysiologic mechanisms

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List of scientific papers developed in the field of the PhD thesis

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1. **A.I. Adamescu**, C. Tilișcan, L. M. Stratan,N. Mihai, O.A. Ganea,S. Ciobanu, A. G. Marinescu, V. Aramă, Ș. Sorin Aramă, *Novel Insights into CKMB, Myoglobin, and Troponin I Levels as Predictors of COVID-19 Severity and Hospitalization Outcomes*, Biomedicines, 2025,13(3),672. Chapter 6, 60-82. https://doi.org/10.3390/biomedicines13030672, ISSN:2227-9059, IF-3,9/2024, Q1.
2. **A.I. Adamescu,** C.Tilișcan, L.M.Stratan, N. Mihai, O.A. Ganea, S.Ciobanu, A.G. Marinescu, V. Aramă, Ș.S. Aramă, *Decoding Inflammation: The Role of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Predicting Critical Outcomes in COVID-19 Patients.* Medicina 2025, 61, 634. Chapter 5, 38-59. https://doi.org/10.3390/medicina61040634, ISSN: 1648-9144, IF- 2,4/2024, Q1

3. **A.I. Adamescu,** C. Tilișcan, L.M. Stratan, N. Mihai, O.A. Ganea, V.D. Miron, S. Ciobanu, V. Aramă, Ș. S. Aramă, *The role of IL-6 and IL-1 in COVID-19 disease progression: the impact of gender-based differences, BMI variability and co-medications.* Farmacia 2025, volumul 73, 2, 2025. Cap. 7, 81-102, https://farmaciajournal.com/issue-articles/the-role-of-il-6-and-il-1-in-covid-19-disease-progression-the-impact-of-gender-based-differences-bmi-variability-and-co-medications/ , ISSN: 2065-0019, IF-1,4/2023, Q4.

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1. **A.I. Adamescu**, C. Tilișcan, O.A. Ganea, S. Ciobanu, D. Mangaloiu, Ș.S. Aramă, V. Aramă, *COVID-19 and influenza- role of haematological parameters in assesing the disease severity,* poster and e-poster paper (P0507) presented at ESCMID Global, 2024, Issue 34, April 27-30, Barcelona, Spain and abstract published in CMI Communications Supplement, September 2024, IF:14,2/2024, Q1. https://doi.org/10.1016/j.cmicom2024.100013

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2. **A. I. Adamescu**, S. Ciobanu, C. Tilișcan, V. Aramă, Ș.S. Aramă, *Associations between inflammatory markers and severe forms of SARS-CoV-2 infection - a retrospective study,* poster paper presented at the National Congress of the Romanian Society of Pathophysiology, October 2-5, 2024, Timisoara, Romania, abstract published in the abstract book of the congress, ISBN 978-606-786-417-5, page 118.

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