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Abstract of dissertation entitled

**Evaluation of biological markers with a
prognostic role in SARS-CoV-2 infection**

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Based on data reported by the World Health Organization (WHO), coronavirus disease 2019 (COVID-19) caused over 7 million deaths worldwide, of which 68,800 in Romania. The overall impact of SARS-CoV-2 infection on the global population, especially in people with comorbidities or at high risk of developing severe clinical form, justified the evaluation of biological markers with a prognostic and predictive role. Etiological diagnosis, early hospitalization, calculation of the risk of unfavorable evolution, efficient use of intensive care services, selection of appropriate therapies, and patient monitoring are essential to ensure a favorable long-term prognosis. Clinical assessment of patients is crucial, but biological markers play an essential role in completing the estimation of infection progression, which ensures improved management, and facilitates personalized therapy. Therefore, current research focuses on identifying prognostic factors that would be able to stratify patients according to the risk of unfavorable evolution for the most appropriate cost-effective management of cases.

Study nr.1. Inflammatory Indices in COVID-19

The aim of the study was to evaluate the inflammatory indices SII (Systemic Inflammatory Index), AISI (Aggregate Systemic Inflammation Index), SIRI (Systemic Inflammatory Response Index) and their dynamic changes in correlation with clinical features, comorbidities, outcomes.

Material and method. This is a retrospective, cross-sectional study on a group of 427 patients confirmed and hospitalized with SARS-CoV-2 infection at the Infectious Diseases Clinic I, Târgu Mureș, between January 2020 and January 2021. Routine tests (complete blood count) were performed upon admission and a second set at an interval of 7-10 days. We calculated the following ratios: SII, SIRI, AISI. Correlations were made with demographic data, patient comorbidities, and disease progression.

Results and conclusions. The mean value of the SII ratio at the first determination (1) was statistically significantly higher in the severe clinical form compared to the moderate forms ($p < 0.001$). We obtained similar results at the second determination (2). In severe forms, the average AISI 1 and 2 ratio was statistically significantly increased ($p < 0.001$). We obtained statistically significant differences between SIRI 1 and 2 and clinical forms ($p < 0.001$). It was found that the average of the ratios studied correlates statistically significantly with clinical evolution. The most valuable seems to be the SII/2 ratio. The means of the SII/1, AISI/1, and SIRI/1 ratios were significantly higher at the time of admission among patients with associated comorbidities, regardless of the clinical form. When evaluating them dynamically, we did not obtain statistically significant differences when comparing patients with or without comorbidities. Patients with comorbidities had a marked inflammatory syndrome from the outset. These calculated ratios are very accessible, inexpensive, and use biological parameters that are determined for each patient. The differences obtained were statistically significant both in correlation with comorbidities and, especially, in terms of evolution. We consider that the SII, AISI, and SIRI ratios are useful for patient stratification, and their dynamic monitoring has a prognostic role.

Study nr.2. Old biological markers in a new conception

Aim of the study. We monitored the number of leukocytes, neutrophils, lymphocytes, platelets, C-reactive protein, the neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and lymphocyte/C-reactive protein ratio, which we correlated with the clinical forms and progression of the disease.

Material and method. This is a retrospective cross-sectional study conducted on a group of 554 adult patients admitted to the Infectious Diseases Clinic I, Târgu Mureș, between January 1 and December 31, 2020, confirmed with COVID-19 by the RT-PCR method. We monitored: white blood cell count, neutrophil count, lymphocyte count, platelet count, serum C-reactive protein level, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, lymphocyte/C-reactive protein ratio. The monitored parameters were correlated with clinical forms and progression.

Results and conclusions. Patients with severe COVID-19 tend to have an increased N/L ratio. This ratio is considered an independent factor of mortality for patients with COVID-19. N/L assessment can also help identify people at high risk of COVID-19, and in outcome risk stratification. In most patients with COVID-19, an increased level of C-reactive protein in serum

was observed. The value of C-reactive protein (CRP) on admission correlated with the severity of the disease and proved to be a good predictor of outcome. Changes in the ratios proposed for the study were statistically significantly correlated with clinical forms. The Tr/L ratio was not significantly different between survivors and deceased, but the N/L and L/CR ratios were clearly different regarding outcomes. Changes in inflammatory biomarkers at the time of hospitalization and during the course of the disease provide important information that allows stratification of patients according to disease severity. These are appreciated in the clinical context, in dynamics and in combination. The use of inflammation markers in a new concept in the form of ratios, their imprinting in our medical thinking would be useful for the most correct assessment of the inflammatory syndrome in COVID-19.

Study nr.3. The Prognostic Utility of Cytokines in Hospitalized COVID-19 Patients

The aim of this study was to investigate the predictive utility of interleukin (IL)-6, IL-8, IL-10, IL-12, tumor necrosis factor alpha (TNF- α), and interferon gamma (IFN- γ) measurement in patients with COVID-19.

Material and Methods: We prospectively enrolled 181 adult patients with COVID-19 admitted to the 1st Infectious Disease County Hospital Târgu Mureș from December 2020 to September 2021. Serum cytokine levels were measured and correlated with disease severity, need for oxygen therapy, intensive care unit (ICU) transfer, and outcome.

Results: We found significantly higher serum levels of IL-6, IL-8, and IL-10 in patients with severe COVID-19 and in those with a fatal outcome. The logistic regression analysis showed a significant predictive value for IL-8 regarding disease severity, and for IL6 and IL-10 regarding ICU transfer and fatal outcome.

Conclusions: Serum levels of IL-6, IL-8, and IL-10 were significantly increased in patients with COVID-19, but their predictive value regarding disease severity and the need for oxygen therapy was poor. We found IL-6 and IL-10 to have a good predictive performance regarding ICU transfer and fatal outcome.

Study nr.4 Dynamic Changes in Lymphocyte Populations and Their Relationship with Disease Severity and Outcome in COVID-19

Aim of the study. The present study aimed to investigate the dynamic changes of lymphocyte subsets in patients with COVID-19.

Material and Methods: 53 patients with COVID-19 were prospectively included, classified as mild, moderate, and severe. The peripheral lymphocyte profiles (LyT, LyB, and NK cells), as well as CD4+/CD8+, CD3+/CD19+, CD3+/NK and CD19+/NK ratios, and their dynamic changes during hospitalization and correlation with disease severity and outcome were assessed.

Results and conclusions. We found significant differences in CD3+ lymphocytes between severity groups ($p < 0.0001$), with significantly decreased CD3+CD4+ and CD3+CD8+ in patients with severe disease ($p < 0.0001$ and $p = 0.048$, respectively). Lower CD3+/CD19+ and CD3+/NK ratios among patients with severe disease ($p = 0.019$ and $p = 0.010$, respectively) were found. The dynamic changes of lymphocyte subsets showed a significant reduction in NK cells (%) and a significant increase in CD3+CD4+ and CD3+CD8+ cells in patients with moderate and severe disease. The ROC analysis on the relationship between CD3+ cells and fatal outcome yielded an AUC of 0.723 (95% CI 0.583–0.837; $p = 0.007$), while after addition of age and SpO₂, ferritin and NLR, the AUC significantly improved to 0.927 (95% CI 0.811–0.983), $p < 0.001$ with a sensitivity of 90.9% (95% CI 58.7–99.8%) and specificity of 85.7% (95% CI 69.7–95.2%). The absolute number of CD3+ lymphocytes might independently predict fatal outcomes in COVID-19 patients and T-lymphocyte subset evaluation in high-risk patients might be useful in estimating disease progression.