

Doctoral thesis summary

Assessing the impact of systemic inflammation in disease modulation in patients with psoriasis

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Psoriasis is a chronic, immune-mediated condition with a significant impact on patients' quality of life. The varied clinical manifestations, lesions' extension, and the debilitating character of the disease are factors that make psoriasis a systemic disease, with a global impact on the patient.

Even though the pro-inflammatory cytokines are important markers of the inflammatory status associated with psoriasis, their routine determination is not an easy one, as it involves high costs and sophisticated laboratory techniques. As such, there is a need to identify reliable laboratory markers, widely available and easily reproducible in clinical activity, with discriminative value in assessing both the severity of the condition and response to various treatments available.

The personal part of this doctoral thesis is structured in four studies. Their main objective was to study the role of inflammatory markers quantified from the blood-count in modulating disease presentation in patients with psoriasis. As such, four research directions were defined, that further converge in the aforementioned major objective. Data from the database of the Dermatovenereology Clinic and the Clinical Pathological Anatomy Service of the Mureș County Clinical Hospital (SCJ) were analyzed. The studies carried out were related to important themes in the literature. Study 1 was carried out using the bibliometric technique, analyzing data from the Web of Science database and analyzed with a dedicated software. Studies 2, 3 and 4 were retrospective studies, that included patients with psoriasis.

The first study was a bibliometric one and aimed to reflect current knowledge status in psoriasis and to identify future research directions in this disease. We evaluated the link between blood-count-derived inflammatory markers and disease presentation in psoriasis, taking into account disease severity and predictive, risk factors, respectively the usefulness of these markers as predictors of liver fibrosis in psoriasis. This doctoral thesis aimed to emphasize the importance of easily obtainable, cost-effective markers in psoriasis, in order to obtain an effective evaluation and follow-up of these patients, and an improvement of their quality of life.

A comprehensive study of the latest scientific developments in a given field can lead to increased accuracy of diagnosis and treatment options. The main objective of this study was to outline the current research field and identify future research directions in psoriasis using bibliometric algorithms based on the hundred most-cited articles related to psoriasis. As such, interest is shifting from clinical aspects to treatment modalities. A special focus is given to innovative therapies, immunological pathways and integrative, complex patient approaches, which represent points of interest in the scientific community and future key topics in research.

The second study aimed to evaluate the usefulness of inflammatory markers quantified from the blood-count as indicators of disease severity in psoriasis and to identify independent prognostic factors of disease severity. 366 adult patients diagnosed with psoriasis vulgaris were retrospectively enrolled, further divided into three study groups. Patients with moderate psoriasis had significantly higher values of leukocytes ($p = 0.004$), neutrophil count ($p = 0.003$), NLR ($p = 0.01$), d-NLR ($p = 0.02$) and SII ($p = 0.009$) compared to those with mild disease and significantly lower values of neutrophil count ($p = 0.01$) and d-NLR ($p = 0.007$) than those with severe disease. WBC, neutrophil count, PLR, NLR, d-NLR, MLR, SII, SIRI and AISI were significantly and positively correlated with disease severity. NLR showed the strongest

correlation ($\rho = 0.30$). If referring to the differentiation of severe from moderate psoriasis, d-NLR is a significant predictor of severe forms ($p = 0.03$), with an AUC of 0.598 and a cut-off value of 2.18. Patients with d-NLR (OR: 0.16, $p < 0.001$), NLR (OR: 4.13, $p < 0.001$) and SII (OR: 1, $p = 0.046$) above the cut-off values of 1.49, 2, 35 and 408.8 respectively have a higher risk of having moderate psoriasis. In addition, values of the aforementioned parameters below the cut-off value are significant predictors of mild psoriasis. If referring to severe psoriasis, a higher level of d-NLR (OR: 0.69, $p = 0.049$) is an independent predictor of advanced forms of the disease. NLR, PLR, d-NLR, MLR, SII, SIRI and AISI are useful indicators of systemic inflammation and disease severity in psoriasis. In addition, d-NLR accurately reflects the negative inflammation associated with this disease and proves to be the most reliable blood-count-derived inflammatory marker in predicting disease severity in all three study groups.

In the third study we evaluated whether blood-count-derived inflammatory markers can serve as predictors of liver fibrosis severity in patients with psoriasis vulgaris. Fibrosis severity was assessed using the FIB-4 index, according to the international consensus. The secondary objective of the present study was to determine whether additional NITs, such as APRI, AAR and GPR, are effective in assessing liver fibrosis in patients with psoriasis vulgaris. 359 patients were included in the study, divided into two study groups based on severity - HR-SF and LR-SF. Patients in the HR-SF group had significantly higher values of ALT, AST, GGT, MLR, APRI, AAR and GPR, while those with LR-SF showed higher levels of WBC, platelets, neutrophils, lymphocytes, PLR, SII, AISI and PWR. PLR, SII, AISI, and PWR were significantly and negatively correlated with liver fibrosis, and MLR, APRI, AAR, and GPR were strongly positively correlated with liver fibrosis. Patients aged over 50 years (OR: 4.63, $p < 0.001$) and having moderate to severe psoriasis (OR: 1.70, $p = 0.028$) were identified as having a higher risk of HR-SF. Moreover, higher levels of MLR (OR: 3.51, $p < 0.001$), APRI (OR: 11.68, $p < 0.001$) and AAR (OR: 13.26, $p < 0.001$), and lower levels of AISI (OR: 0.98, $p = 0.009$) and PWR (OR: 0.94, $p < 0.001$) were independent predictors of significant liver fibrosis. MLR, PWR and AISI have been identified as useful prognostic factors for assessing the severity of liver fibrosis in psoriasis. In addition, APRI and AAR can be used as additional non-invasive markers for the evaluation of liver fibrosis. These results bring new information and highlight once again the link between psoriasis, systemic inflammation and associated comorbidities.

The fourth study assessed the role of eosinophil-derived inflammatory markers as predictors of psoriasis severity and determined significant cut-off values. 366 patients with psoriasis vulgaris were included. Eosinophil/monocyte (EMR), eosinophil/neutrophil (ENR) and eosinophil/lymphocyte (ELR) ratios were tested. For discrimination between mild and moderate to severe psoriasis, all markers were found to be statistically significant ($p < 0.05$). Strictly referring to reference to markers quantified from eosinophil count, EMR had higher sensitivity and ENR higher specificity. Therefore, values greater than the cutoff values of 6.25 for WBC and 3.64 for neutrophil count can confidently predict a moderate-severe form of disease. On the other hand, if referring to EMR, ENR, lymphocyte and eosinophil count, it appears that values below the cut-off values of 0.34, 0.03, 1.7 and 0.05, respectively, adequately predict a milder form of psoriasis. The number of eosinophils and derived inflammatory markers, EMR and ENR, are reliable indicators of systemic inflammation and disease severity in psoriasis. In addition, ENR proves to be the most reliable inflammatory marker derived from eosinophil count in predicting disease severity in the two study groups.

