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**OP0237 USE OF NEUTROPHIL/LYMPHOCYTE AND PLATELET/LYMPHOCYTE RATIOS TO DETECT SYSTEMIC SCLEROSIS-ASSOCIATED INTERSTITIAL LUNG DISEASE**

**Keywords:** Systemic sclerosis, Diagnostic tests, Biomarkers

**Background:** Intestinal lung disease (ILD) remains a main cause of morbidity and mortality in patients with systemic sclerosis (SSc). New markers to early detection of SSc-ILD are an unmet need [1]. Neutrophil/lymphocyte (NLR) and platelet/lymphocyte (PLR) ratios have emerged as potential biomarkers of systemic inflammation in cancer, cardiovascular disorders, infections and rheumatic diseases [2].

Recently, some studies in South Korea and Turkey have shown correlation of NLR and PLR with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), disease activity, pulmonary and cutaneous involvement in SSc [3,4]. However, manifestations of SSC present variability in different populations. Could NLR and PLR be used as new biomarkers to detect SSc-ILD in Mexican-Mestizo population?

**Objectives:** To investigate the usefulness of NLR and PLR to detect SSc-ILD.

**Methods:** A cross-sectional study, where patients > 18 years of age with a diagnosis of SSc according to EULAR/ACR 2013 criteria and diagnosis of ILD by forced vital capacity (FVC) < 70% and > 5% of affected lung area by diffuse ground-glass opacity or pulmonary fibrosis on high-resolution computed tomography (HRCT) were included. Patients with corticosteroid use, malignancy, iron deficiency anemia and active infections were excluded.

**Results:** Of 74 patients with SSc 94.6% were women. The mean age [standard deviation (SD)] was 49.8 (14.1) years. The median of disease duration [inter-quartile range quartile 25-75 (IQR)] was 7 (4.7-12) years and subtype of limited cutaneous SSc (p=0.001). For NLR, the cut-off value (COV) was 2.05 and the area under the curve (AUC) was 0.887, with sensitivity, specificity and DA of 97.1%, 71.1% and 81.1% respectively (Figure 1). For PLR, the COV was 184.54 and the AUC was 0.743, with sensitivity, specificity and DA of 58.3%, 89.5% and 74.3%, respectively (Figure 2). A strong correlation with FVC (r=0.527) and EUSTAR activity index (r=0.513) was observed. Moderate correlation with PLR (r=0.696) and affected lung area on HRCT (r=0.654) and moderate correlation with FVC (r=0.502) and EUSTAR activity index (p=0.051). In contrast, PLR only had a weak correlation with EUSTAR activity index (p=0.371; p<0.001). MLRA showed that NLR > 2.05 (OR 5.42, 95% CI 1.38-18.46, p=0.003) remained associated with an increased risk of SSc-ILD.

**Conclusion:** This study suggests that NLR show better DA than PLR, as well as it can be a useful screening tool and a low-cost biomarker to detect SSc-ILD in Mexican-Mestizo patients. Also, NLR is associated with an increased risk of SSc-ILD and present a good correlation with affected lung area on HRCT, FVC and disease activity. However, these observations must be confirmed in larger and prospective studies.

**REFERENCES:**


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**OP0238 IMMUNOSUPPRESSION WITH TARGETED DMARDS REDUCES MORBIDITY AND MORTALITY IN PRE-CAPILLARY PULMONARY HYPERTENSION ASSOCIATED WITH SYSTEMIC SCLEROSIS: A EUSTAR ANALYSIS**

**Keywords:** bDMARD, Systemic sclerosis, Lungs

**Background:** In the last years, research has focused on the characterization of pre-capillary pulmonary hypertension (pPH) as a potential candidate of systemic sclerosis (SSc), mainly due to the positive outcomes of immunosuppression with targeted drugs in clinical practice and randomized clinical trials [1-5]. The aim of this study was to evaluate the effectiveness of immunosuppression with targeted DMARDs (bDMARD) in a large cohort of SSc-pPH patients included in the EUSTAR database.

**Methods:** Patients included in the EUSTAR registry with SSc-pPH (primary or secondary) and started bDMARD therapy before or after disease diagnosis were included. The primary endpoint was defined as the time to death, transplantation or the occurrence of other events of interest (complications, hospitalization, VAQ, death, etc.) through the EUSTAR cohort. Time to event was defined as the time from first bDMARD treatment until the event of interest. An event-related Cox model was used to estimate the hazard ratio (HR) and its 95% confidence interval (CI) adjusted for age, gender, disease duration, smoking status, presence of antinuclear antibodies, and comorbidities related to pPH.

**Results:** At the beginning of the study, the database included 16,612 patients, of which 1,237 (7.4%) had SSc-pPH. Among them, 657 (53.5%) received an immunosuppressive treatment with bDMARDs. The median time between disease diagnosis and immunosuppressive treatment was 3.4 years (IQR 1.5-7.6). The median age at immunosuppressive treatment was 52.4 years (IQR 45.3-60.8). The median disease duration at immunosuppressive treatment was 2 years (IQR 1.1-3.5). The most used bDMARDs were rituximab (29.2%) followed by tocilizumab (22.2%) and abatacept (13.8%). The primary endpoint occurred in 260 patients (39.7%) during a median follow-up of 5.4 years (IQR 3.3-7.5). The multivariate analysis showed that the use of bDMARDs was associated with a lower risk of the primary endpoint (HR 0.67, 95% CI 0.53-0.85, p=0.001).

**Conclusion:** Immunosuppression with targeted DMARDs (bDMARD) reduces the risk of morbidity and mortality in pre-capillary pulmonary hypertension associated with systemic sclerosis (SSc).

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Background: Pre-capillary pulmonary hypertension (pulmonary hypertension) affects 9-15% of patients with systemic sclerosis (SSc) and may be associated with interstitial lung disease (ILD) of variable extent. Immunosuppressants (IMS) are standard of care for treating ILD, skin or musculoskeletal manifestations in SSc. However, their beneficial effect on pPH remains unclear.

Objective: To determine whether exposure to IMS in SSc-pPH affects morbidity and mortality in the EUSTAR cohort.

Methods: In the approved EUSTAR project CP11, we included SSC patients with pPH (mPAP ≥21 mmHg, PVR ≤15 mmHg + 75% vs PVR ≤2) with data on IMS (cSMDARs - prednisone ≥10mg/d, cyclophosphamide, mycophenolate mofetil, azathioprine, methotrexate; targeted therapies: abatacept, rituximab, tocilizumab, TNFI, JAKI), pulmonary arterial hypertension (PAH) medications (bosentan, macitentan, ambrisentan, sildenafil, tadalafil, riociguat, selexipag, prostanoids) and at least 3 months follow-up after pPH diagnosis. We considered exposure to a drug if it was ongoing at or prescribed after pPH diagnosis and administered for at least 30 days. Patients were clustered into group 1 or group 3 pPH based on ILD presence on HRCT and FVC ≤70%, as proposed in the INCREASE trial. The morbidity-mortality outcome was defined by the first event between death or pPH worsening (following the SERAPHIN trial: one of ≥15% 6MWD decrease, worsening of NYHHA class, onset of right heart failure, additional PAH medication, starting iv-sc prostanoids, lung transplantation, atrial septostomy). We evaluated the association between IMS and time to first event with a multiple Cox regression model for time dependent covariates, with robust Sandwich variance estimate and backward selection. The baseline confounders were chosen on experts’ opinion and included SSc-related risk factors for mortality or IMS prescription (sex, age, diffuse skin subtype, renal crisis, digital ulcers, muscle weakness, joint synovitis, ILD on HRCT, LVEF%, FVC%, DLCO%) and PAH risk stratification parameters (mPAP, increased INRNP/TnpBNP, NYHHA class II, reduced cardiac index, reduced 6MWD). PAH medications (none, mono, double or triple therapy) were also included as time-dependent confounder.

Results: 55 SSc-pPH-PAH patients from 54 EUSTAR centers were included (18% males, age 53±11 years, disease duration 11±8 years, 29% diffuse skin subset, 60% ILD on HRCT; 377 (50%) received IMS [365 (47%) cSMDARs, 68 (9%) targeted therapies] and 642 (85%) PAH medications. Patients treated with IMS had more frequently ILD (78 vs 43%), diffuse skin (41 vs 18%), joint (16 vs 7%) and muscle (22 vs 10%) involvement. In 2.9 (12.5-4.4) years median follow-up, 546 (70%) patients developed a morbidity-mortality event. While overall IMS exposure did not associate with the outcome, targeted therapies were associated with reduced risk of mortality-mortality (HR 0.59 [95% CI 0.36-0.96], p=0.04; Figure 1a).

Conclusion: When clustering into group 1 [n=561, 40% IMS, n=32 (6%) targeted therapies] or group 3 [n=194, 80% IMS, n=36 (19%) targeted therapies], less morbidity-mortality events were recorded for group 1 (69 vs 81%). Despite the rarer use, the protective effect of targeted therapies for morbidity-mortality was confirmed in group 1 (HR 0.24, 95% CI 0.02-0.64, p=0.01, Figure 1b) but not in group 3 (Figure 1c). When looking at specific target therapies, a risk reduction for the morbidity-mortality outcome was noted for tocilizumab [in the whole cohort (n=163, 66% cSMDARs, 18% targeted therapies) one of ≥15% 6MWD decrease, worsening of NYHA class, onset of right heart failure, additional PAH medication, starting iv-sc prostanoids, lung transplantation, atrial septostomy]. We evaluated the association between IMS and time to first event with a multiple Cox regression model for time dependent covariates, with robust Sandwich variance estimate and backward selection. The baseline confounders were chosen on experts’ opinion and included SSc-related risk factors for mortality or IMS prescription (sex, age, diffuse skin subset, renal crisis, digital ulcers, muscle weakness, joint synovitis, ILD on HRCT, LVEF%, FVC%, DLCO%) and PAH risk stratification parameters (mPAP, increased INRNP/TnpBNP, NYHHA class II, reduced cardiac index, reduced 6MWD). PAH medications (none, mono, double or triple therapy) were also included as time-dependent confounder.

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Does early immunosuppressive therapy prevent systemic sclerosis associated interstitial lung disease?

Keywords: Systemic sclerosis, Lungs, Epidemiology

A. Velauthapillai1, M. Bootsma1, C. Bruni2, O. Distler2, C. Van den Ende1, M. Vonk1,3, R. W. W. de Jongh1, A. Velauthapillai: None declared, Merle Bootsma: None declared, Cosimo Bruni Speakers bureau: Eli Lilly, Consultant of: Eli Lilly, Grant/research support from: Gruppo Italiano Lotta alla Sclerosi Poliarticolare (EUSTAR), Foundation for research in Rheumatology (FOREUM), Sclerodermia Clinical Trials Consortium (SCCTC), Educational grants from Abbvie, Lilly, Merck, Pfizer, Roche, Consultant of: ABBvie, Janssen, Boehringer-Ingerlheim, Grant/research support from: Actelion, Biogen, Boehringer, CSL Behring, Corbus, Galapagos, Mitsubishi, Medscape, Merck, Pfizer, Roche, Consultant of: Actelion, Biogen, Boehringer, CSL Behring, Corbus, Galapagos, Mitsubishi, Medscape, Merck, Pfizer, Roche, Gabriela Riekmasten: None declared, Carmen Pilar Simeon Aznar: None declared, Jeska de Vries-Bouwstra Speakers bureau: ABBVie, Biogen, Boehringer-Ingelheim, Consultant of: ABBVie, Biogen, Boehringer-Ingelheim, Grant/research support from: ABBVie, Biogen, Boehringer-Ingelheim, Janssen-Cilag, Galectos, Roche, 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Janssen, Novartis, Simona Rednic: None declared, Petros Smakakis: None declared, Yair Levy: None declared, Vivian Hsu: None declared, Stefan Heitmann: None declared, Jörg Hennes Speakers bureau: Abbvie, Boehringer Ingelheim, GSK, BMS, Janssen, Novartis, Pfizer, UCB, Consultant of: Abbvie, Boehringer Ingelheim, GSK, BMS, Janssen, Novartis, Pfizer, UCB, Gianluca Moroncini: None declared, Michele Judicini: None declared, Ellen De Langhe: None declared, Ariane Herrick: None declared, Carlomaurizio Montuccio: None declared, Anna-Maria Hoffmann-Vold Speakers bureau: ehringer Ingelheim, Janssen, Medscape, Merck Sharp & Dohme and Roche, Consultant of: ARXX, Boehringer Ingelheim, Genentech, Janssen, Medscape, Merck Sharp & Dohme and Roche, Grant/research support from: Boehringer Ingelheim, Janssen, Oliver Distler Speakers bureau: 4P-Pharma, Abbvie, Acceleron, Alcimed, Alcimed, Altavant, Amgen, AnaMar, Arxx, AstraZeneca, Blade, Bayer, Boehringer Ingelheim, Corbus, CSL Behring, Galderma, Galapagos, Glenmark, Gossamer, IQvia, Kymera, Lupin, Medscape, Merck, Menilteny Biotec, Mitsubishi Tanabe: Novartis, Prometheus, Redxpharma, Roivant and Topadur in the area of potential treatments of scleroderma and its complications,, Consultant of: 4P-Pharma, Abbvie, Aceleror, Alcimed, Alcimed, Altavant, Amgen, AnaMar, Arxx, AstraZeneca, Blade, Bayer, Boehringer Ingelheim, Corbus, CSL Behring, Galderma, Galapagos, Glenmark, Gossamer, IQvia, Kymera, Lupin, Medscape, Merck, Menilteny Biotec, Mitsubishi Tanabe: Novartis, Prometheus, Redxpharma, Roivant and Topadur in the area of potential treatments of scleroderma and its complications,, Consultant of: 4P-Pharma, Abbvie, Aceleror, Alcimed, Alcimed, Altavant, Amgen, AnaMar, Arxx, AstraZeneca, Blade, Bayer, Boehringer Ingelheim, Corbus, CSL Behring, Galderma, Galapagos, Glenmark, Gossamer, IQvia, Kymera, Lupin, Medscape, Merck, Menilteny Biotec, Mitsubishi Tanabe: Novartis, Prometheus, Redxpharma, Roivant and Topadur in the area of potential treatments of scleroderma and its complications. 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Background: Systemic sclerosis (SSc) is an autoimmune disease characterized by a triad of inflammation, vascular damage and fibrosis. Interstitial lung disease (ILD) is a major contributor to impaired quality of life and a leading cause of death in these patients. While recent studies reported a favorable effect on disease course when starting immunosuppressive (IMS) therapy in mild and moderate ILD, no definite evidence of a preventive mechanism of IMS therapy for ILD onset is established (1, 2).

Objectives: The objective of our study was to explore the association between timing of start IMS therapy and the development of ILD.

Methods: A combined cohort was created from the EUSTAR database and Nijmegen Systemic Sclerosis cohort, including patients: 1) aged 18 years or older 2) treated with IMS (i.e. mycophenolate mofetil, metoxetur, cyclophosphamide and rituximab) after SSc diagnosis 3) negative for signs ofILD on high-resolution CT (HRCT) at or within 2 months after start treatment and 4) no prior treatment with biological or antifibrotic in the preceding years. Data between start of first IMS treatment and five years follow-up were analysed. Disease duration (time between first non-Raynaud phenomenon and start IMS) was dichotomized into early and late treatment using a cut-off point of 3 years. ILD-free survival (absence of HRCT confirmed ILD diagnosis) was assessed with unadjusted Kaplan-Meier analysis on complete cases and a Cox proportional hazard analysis on imputed data adjusting for confounders.

Results: We identified 1037 patients meeting the eligibility criteria. The early treatment group (n=539, 52 %) showed a higher prevalence of male sex, dif- fuse cutaneous SSc (dcSSc, 52.9% vs 36.4%, p= 0.001), anti-topoisomerase I antibody positivity (ATA, 51.0% vs. 42.5%, p= 0.01), anti-RNA polymerase III antibody positivity (ARA, 11.7% vs. 5.4%, p=0.009) and elevated C-reactive protein levels (30.6% vs. 22.6%, p=0.03). Further, patients in the early group had a higher modified Rodnan skin score (mRSS, mean(SD) 13.9(7.9) vs. 9.7(8.9), p= 0.001). The incidence of ILD was 46.1% after mean(SD) 3.6(14) years of treatment and not significantly different between the groups (mean(95% CI): early: 47% (43-51) vs. late: 45%(40-50), p= 0.64). The unadjusted Kaplan-Meier survival curve on complete cases (Figure 1) shows no differences in ILD-free survival rates between the early and late treatment group. The hazard ratio for ILD in the early treatment group was 1.11 (95% CI: 0.91-1.36) adjusting for gender, dcSSc, Caucasian ethnicity, ATA, ARA, age, forced vital capacity and diffusing capacity for carbon monoxide at baseline.

Conclusions: Our finding did not confirm a preventive role of early vs. late timing of IMS therapy on ILD development. However, our findings should be interpreted with caution, considering the high inflammatory, ATA-positive enriched nature of the cohort selected, as well as confounding by indication, which cannot be ruled out also after adjusting for other confounding factors.

References:

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Figure 1. Kaplan-Meier curve of ILD-free survival estimates. Survival rate with 95% confidence interval is shown for the early and late treatment group.

Conclusion: Our finding did not confirm a preventive role of early vs. late timing of IMS therapy on ILD development. However, our findings should be interpreted with caution, considering the high inflammatory, ATA-positive enriched nature of the cohort selected, as well as confounding by indication, which cannot be ruled out also after adjusting for other confounding factors.