on upper extremities. None of patients had allodynia, but impaired vibratory sensibility was found in all patients with NP. Clinical signs of radiculopathy were present in 6 patients. Hypoesthesia was registered in typical dermatomes in 6/11 (54.5%) of patients, with asymmetric hyporeflexia in 2/11 (18.1%) patients on lower, and none of patients on upper extremities. Despite the fact that almost every patient had symptoms and signs suggesting polyneuropathy, in only four of them demyelinating polyneuropathy was detected by ENG.

Conclusions: NP is common in patients with SSc. Presence of NP is associated with more severe SSc, symptoms of depression and worse quality of life. Almost all SSc patients (90.9%) with NP have typical symptoms and signs for polyneuropathy. However, in only few of them polyneuropathy could be detected by ENG. This finding suggests that pure small-fiber polyneuropathy, which is not detectable by ENG, may be the cause of NP in most of patients.

Disclosure of Interest: None declared

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FRI0406   **MORTALITY PROFILE IN SYSTEMIC SCLEROSIS: A LARGE RETROSPECTIVE POPULATION-BASED STUDY FROM BRAZIL**

R.P. Rezende [1], R. Gismondi [1], H. Maleh [1], M.L. Rosa [2], R. Ramos [1], L.O. Mocarzel [1]. [1]*Clinical Medicine;* [2]*Epidemiology and biostatistics, Universidade Federal Fluminense, Niterói-RJ, Brazil*

Background: Systemic sclerosis (SSc) is an uncommon autoimmune multisystem disease associated with reduced life expectancy compared with the general population.[1] In order to prolong survival of this patient population, clear information on the most important death-related conditions is undoubtedly necessary. No mortality data in SSc, however, are available from Latin America, as well as few large series studies have looked at the mortality profile in SSc.

Objectives: We aimed to describe the causes of death in SSc occurred in the state of Rio de Janeiro, Brazil, from 2006–2015, and also to compare the data gathered with the general population mortality.

Methods: All death certificates issued in the state of Rio de Janeiro, Brazil, from 2006–2015 were screened for the code attributed to SSc according to the tenth revision of the International Classification of Diseases (ICD-10), either as an underlying (UD) cause of death (also referred to as basic cause of death) or a non-underlying (non-UD) cause. In addition to compiling the causes of death in both settings, we calculated the non-adjusted as well as the age bracket-adjusted (age at death <50 years and ≥50 years) mortality ratio against the general population for each cause of death when SSc was listed as a non-UD cause.

Results: Of 1.294.491 fatalities recorded over the study period, ICD-10 code for SSc was listed on 374 (0.02%) death certificates, being a basic cause of death on 223 occasions and a non-UD cause on 151 occasions. The overall mean (SD) age at death in SSc was 58.7 (15.6) years, with men (n=56) having an earlier mean age at death than women (n=318) [53.5 vs 59.6 years, respectively; p=0.004]. For SSc as a basic cause of death, the main non-UD causes were respiratory system diseases (61.4%), in particular pneumonia, followed by septicemia (37.6%), diseases of the circulatory system (34.9%), and renal failure (9.4%). There were no significant differences between the genders for each cause of death. The mean age at death was significantly lower among men vs women for diseases of the respiratory system, respiratory failure, certain infectious and parasitic diseases, and septicemia. For SSc as a non-UD cause of death, the major conditions leading to death were circulatory system diseases (39%), in particular pulmonary arterial hypertension (PAH; 13.2%), followed by certain infections and parasitic diseases (11.9%), malignant neoplasms (10.5%) and diseases of the digestive system (9.9%). Compared with the overall population, patients with SSc had an excess of death (odds ratio [OR] >1) due to PAH (OR 138.94), septicemia (OR 1.92), gastrointestinal hemorrhage (OR 2.40), other systemic connective tissue diseases (OR 24.78) and pulmonary fibrosis (OR 11.05), as well as due to heart failure (OR 6.40) for deaths occurred before age 50.

Conclusions: We have shown large data on the mortality profile of patients with SSc, the first from Latin America. Of note, infections and cardiorespiratory diseases had a strong impact on mortality, as evidenced by previous publications.[1] Taking all into account, these data support an increased vigilance for infections, as well as the need to implement effective measures to control modifiable cardiovascular risk factors, including screening for PAH.

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FRI0407   **MACROVASCULAR INVOLVEMENT IN SYSTEMIC SCLEROSIS PATIENTS: IS THERE A RELATIONSHIP WITH MICROVASCULAR PERIPHERAL BLOOD FLOW?**

S. Paolino [1], B.M. Colombo [2], B. Ruaro [1], E. Gotelli [1], A. Sulli [1], M. Ghio [1], C. Pizzorni [1], E. Alessandri [1], M. Patanè [1], M. Cutolo [1]. [1]*Department of Internal Medicine, University of Genova, IRCCS AOU San Martino, Genoa, Italy, Research Laboratory and Academic Division of Clinical Rheumatology;* [2]*IRCCS AOU San Martino, Genoa, Italy, Genoa, Italy*

Background: Raynaud's phenomenon and digital ulcers are common clinical skin manifestations of the microvascular dysfunction in systemic sclerosis (SSc).

Although microvascular and macrovascular abnormalities frequently coexist in disease such as diabetes mellitus and other vascular diseases, the possible association between microvascular failure and macrovasculopathy in SSc patients has not been deeply investigated (1).

Objectives: The aim of the study was to estimate in SSc patients the macrovascular function by measuring of the Intima-Media Thickness (IMT) of high-caliber and periferic small-caliber arteries, and to evaluate the possible correlation with microvascular blood perfusion (BP) assessed by Laser Speckle Contrast Analysis (LASCA).

Methods: Twenty-nine female SSc patients (mean age 65.7±12.07 SD years, mean disease duration 97.3±68.01 SD months) were enrolled after informed consent. Carotid IMT was evaluated through B-mode US imaging (Esaote, Genoa) using transducer 18 MHz on both right and left common carotid arteries (CCA) as well as ulnar (UA) and radial arteries (RadA). Therefore, an average IMT score was obtained for any evaluated site. Peripheral BP was assessed by LASCA (Perimed-Sweden) at the level of fingertips, periungueal areas, dorsum and palm of both hands, and face. The BP values were reported as perfusion units (PU) (2). In addition nailfold videocapillaroscopy (NVC) in order to assess the microvascular morphological status was done by nailfold video capillaroscopy (NVC) considering the different progressive SSc patterns and the microangiopathy evolution score (MES) (3–4).

Results: A positive correlation was observed between CCA IMT and age (p=0.004) and disease duration (p=0.02). On the other hand, no significant correlations were observed between IMT of periferic small-caliber arteries (UA and RadA) and age or disease duration. Positive correlations were found between microvascular damage, as assessed by MES and IMT at the level of periferic small-caliber arteries. No significant correlation was observed between macrovascular involvement of high-caliber arteries and peripheral BP as assessed by LASCA. However, at the peripheral site a correlation was observed between RadA IMT and palm (p=0.05), periungueal (p=0.04) and dorsum of hand BP (p=0.0006), as assessed by LASCA. UA IMT showed a correlation limited to the dorsum of the hand (p=0.003).

Conclusions: Significant correlations seem to exist between increased IMT of periferic small-caliber arteries (macrocirculation) and altered peripheral BP (LASCA) at the level of hand microvessels (microcirculation) in SSc patients. These results were found strength by a further correlation with the microvascular damage (MES).

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FRI0408   **NEOPTERIN AS A SEROLOGICAL MARKER OF DISEASE ACTIVITY IN PATIENTS WITH ANTI-MELANOMA DIFFERENTIATION-ASSOCIATED GENE 5 ANTIBODY POSITIVE CLINICALLY AMYOPATHIC DERMATOMYOSITIS**

S. Tsunoda, A. Nishioka, T. Abe, M. Kitano, K. Matsui, H. Sano. *Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan*

Background: Anti-melanoma differentiation-associated gene 5 (MDA5) antibody in clinically amyopathic dermatomyositis (CADM) is associated with rapidly progressive interstitial lung disease (RPILD). RPILD is a rare disorder with a bad outcome, and therefore the intensive treatment with combinational immunosuppressive drugs in addition to steroid need to be initiated. However until now, good serological markers to evaluate disease activity in CADM have not been established. Activated alveolar macrophage is one of the possible candidates worsening the condition of RPILD.

Objectives: To investigate new serological markers of disease activity in anti-MDA5 antibody positive CADM for therapeutic indication.

Methods: Thirteen anti-MDA5 antibody positive CADM patients were enrolled. We serially measured serum anti-MDA5 antibody, and neopterin and IL-18 as markers of activated macrophage by serum enzyme-linked immunosorbent assay. We tracked them at three points in each patients: before treatment, soon after a series of intravenous cyclophosphamide pulse therapy (about 3months later after onset) and the remission status (about one year later after onset).

Results: Four patients died soon after the initial treatment because of the deterioration of RPILD. At onset of the disease, the levels of serum anti-MDA5 antibody and neopterin were extremely high (169.75±24.3 index and 27.6±24.1 nmol/l) in all patients. However serum IL-18 level was almost normal (479.3±301.4 pg/ml). Among the 9 surviving patients, it took about one year for anti-MDA5 antibody level to decrease to the normal range. On the other hand, neopterin level decreased quickly after the initial treatment. The level of anti-MDA5 antibody transitioned from 169.75±24.3 index to 93.1±50.1 index, and then to 44.8±45.4 index (P=0.003). Neopterin level transitioned from 27.6±24.1 nmol/l to 9.1±6.5 nmol/l, and then to 6.4±5.0 nmol/l (P=0.006). IL-18 level transitioned from 479.3±301.4 pg/ml to 246.0±175.8 pg/ml, and then to 233.3±180.1 pg/ml (P=0.02). The level of anti-MDA5 didn't correlate with the level of ferritin (r=0.28), neopterin (r=0.16), IL-18 (r=0.06) and soluble IL-2 receptor (r=0.27), but the level

of neopterin was well correlated with the level of ferritin (r=0.95), IL-18 (r=0.77) and soluble IL-2 receptor (r=0.75).

Conclusions: Anti-MDA5 antibody titer is useful if the patients could reach and maintain the remission or not. Serum neopterin level is useful to predict the clinical status at present for therapeutic indication.

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FRI0409   **OSTEONECROSIS OF THE LUNATE BONE ASSOCIATED TO SYSTEMIC SCLEROSIS**

M. Llop Vilaltella, S. Zegarra Mondragón, W.A.A. Sifuentes Giraldo, C. de la Puente Bujidos, M. Vázquez Díaz. *Rheumatology, Ramon y Cajal University Hospital, Madrid, Spain*

Background: Osteonecrosis of the lunate bone (OLB), also known as Kienböck's disease, is a rare disorder that has been recently reported in several patients with systemic sclerosis (SSc)[1], but still it is not clear if this is only a coincidence of 2 rare disdorders or whether OLB is a potentially under-recognized manifestation of SSc.

Objectives: To describe the clinical features of patients with SSc seen in a Spanish tertiary care center, who develop OLB.

Methods: We performed a retrospective observational study that included patients followed in our center between January 2010 and December 2015. Demographic data, clinical and laboratory features, risk factors for osteonecrosis, imaging, treatment and outcome were collected.

Results: A total of 115 SSc patients were identified and 4 of them (3.47%) developed OLB. Mean age of these patients was 59.5 (range: 52–73), being all women. 2 cases were limited cutaneos SSc (lcSSc) and 2 cutaneous diffuse SSc. 3 cases showed anticentromere antibodies and 1 anti-topoisomerase I antibodies, but none presented anticardiolipin antibodies nor had previous thrombotic events. Mean disease duration was 13.5 years (range: 7–17). One patient was ex-smoker, but none had alcohol consumption, and one case was hypertensive. All patients had vascular manifestations (severe Raynaud phenomenon, digital ulcers in treatment with endothelin antagonists and perfusion of iv prostaglandins, and one case had critical digital ischemia); all the patients showed calcinosis in the upper limbs, and they also had joint involvement (50%), gastrointestinal (100%), and pulmonary (50%) manifestations. History of rolonged corticosteroid therapy at low doses (prednisone 5–10 mg/day) was present in all cases and was discontinued one year before the onset of osteonecrosis in one case. OLB was unilateral right in 3 cases and bilateral in one case. The patients presented with clinical pain and/or swelling in the affected wrist in the months prior to diagnosis of OLB, which was evidenced by simple radiography, MRI and bone scintigraphy. One of the cases also showed extensive synovitis in the affected wrist and another one developed collapse of the lunate bone with displaced fragment and edema. Treatment was surgical in 25% of the cases (proximal carpectomy), and conservativein in the rest. Among the total SSc population studied there was another case of lcSSc presenting osteonecrosis of the left tarsal scaphoid bone.

Conclusions: A total of 15 cases of OLB associated to SSc have been reported to date, so it could be an underestimated disease-associated feature of SSc. It has been suggested that its etiology is linked to SSc-related vasculopathy and all our cases had evidence of severe vasculopathy. The location and vascularization of the lunate bone should be taken into account, since no case developed osteonecrosis in other common locations despite corticotherapy, and complete occlusion of the distal ulnar artery has been reported in 3 cases of the literature. The presence of pain, with or without wrist inflammation in SSc patients should make us consider OLB, which is probably more frequent than expected, especially when there is evidence of severe SSc-related vasculopathy.

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FRI0410   **PREDICTORS OF MORBIDITY AND MORTALITY IN PATIENTS WITH EARLY SYSTEMIC SCLEROSIS: LONG-TERM FOLLOW-UP FROM A SINGLE CENTRE INCEPTION COHORT STUDY**

S. Panopoulos, V.-K. Bournia, G. Konstantonis, K. Fragiadaki, P.P. Sfikakis, M.G. Tektonidou. *First Department of Propedeutic and Internal Medicine and Joint Academic Rheumatology Program, National and Kapodistrian University, Medical School, Athens, Greece*

Background: Several studies have investigated the predictors of morbidity and mortality in Systemic sclerosis (SSc). However long-term follow-up data from inception cohorts of early SSc patients are limited.

Objectives: To identify predictors of morbidity and mortality in a single centre inception cohort of early SSc patients at long-term follow-up.

Methods: Our inception cohort comprised SSc patients who fulfilled the American College of Rheumatology criteria, were recruited within 12 months of disease onset and followed prospectively for at least 3 years. Clinical manifestations, laboratory and lung function tests were recorded for each patient at baseline and at 3rd and 6th years of follow up. Multivariate regression analysis and Cox proportional hazard models were used to identify predictors (clinical manifestations, laboratory and lung function tests at baseline) of morbidity and mortality in SSc, respectively.

Results: A total of 114 patients (96 female, mean age at diagnosis 48.1±13.5 years, 53 diffuse SSc subtype) were included in the study, from January 1997 to December 2012. All patients were followed for at least 3 years and 84 patients for at least 6 years. Twenty (17.5%) of 114 patients died during a mean follow up of 101.8±48.5 months. In multivariate regression analysis predictors for major SSc outcomes at 6 years were: diffuse subtype (OR: 6.2, p=0.015), anti-scl-70 positivity (OR: 3.9, p=0.05), esophageal involvement (OR: 6.5, p=0.017) and digital ulcers (OR: 8.6, p=0.003) at baseline for the development of pulmonary fibrosis (PF). The presence of digital ulcers at baseline was a predictor for the development of arrhythmias (OR: 3.7, p=0.05) and the presence of arrhythmias at baseline for the development of pulmonary hypertension (PH) (OR: 5.4, p=0.039). Cox proportional hazard models multivariate analysis revealed that independent predictors of mortality were: male gender (HR: 3.3, p=0.023), diffuse type (HR: 8.7, p=0.004), PF at baseline (HR: 2.7, p=0.05), PH based on echocardiography at baseline (HR: 12.7, p=0.001) FVC <80% (HR: 2.74, p=0.042) and DLCO <60% of predicted value at baseline (HR: 2.97, p=0.019).

Conclusions: Results from long-term follow-up data from a single centre inception cohort indicate that diffuse SSc subtype, anti-Scl-70 positivity, esophageal involvement and digital ulcers at baseline are independent predictors for the development of PF. Male gender, diffuse subtype, PF, PH and decreased FVC and DLCO at baseline are prognostic factors of mortality.

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FRI0411   **COADMINISTRATION OF BOSENTAN HAS NO EFFECT ON THE PHARMACOKINETICS OF NINTEDANIB**

S. Wind[1], G. Simons[1], J. Bertulis[1], C. Coeck[2]. *[1]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; [2]SCS Boehringer Ingelheim Comm.V., Brussels, Belgium*

Background: Nintedanib is a potent intracellular inhibitor of tyrosine kinases that has been approved for the treatment of idiopathic pulmonary fibrosis and is being investigated as a treatment for interstitial lung disease associated with systemic sclerosis (SSc-ILD). Bosentan is a dual endothelin receptor antagonist used in the treatment of pulmonary arterial hypertension, which is a common comorbidity of SSc-ILD.

Objectives: To ascertain the effect of bosentan on the pharmacokinetics of nintedanib.

Methods: In an open-label, single-centre study, healthy male subjects aged ≥18 and ≤55 years with a body mass index (BMI) ≥18.5 and ≤29.9 kg/m² received a single dose of nintedanib 150 mg alone (period 1) followed by bosentan 125 mg twice daily (bid) for 8 days (bosentan loading dose phase on days 1–6) with a single dose of nintedanib 150 mg on day 7 (period 2). The primary endpoints were the maximum plasma concentration (C_{max}) of nintedanib and the area under the plasma concentration-time curve from time 0 to the last quantifiable concentration (AUC_{0-tz}) of nintedanib. The secondary endpoint was the AUC from time 0 extrapolated to infinity ($AUC_{0-\infty}$) for nintedanib.

Results: Thirteen subjects (12 White; mean [SD] age 35.0 [9.8] years and BMI 24.5 [2.5] kg/m²) were treated. All subjects completed the planned observation period. Based on C_{max}, AUC_{0-tz} and $AUC_{0-\infty}$, exposure to nintedanib was similar after a single dose of nintedanib given alone or in combination with multiple doses of bosentan 125 mg bid (Table). Adverse events were reported in 4 subjects (30.8%) on nintedanib alone (period 1), 4 subjects (30.8%) on bosentan 125 mg bid (days 1–6 of period 2) and 2 subjects (15.4%) after administration of bosentan with nintedanib (days 7 and 8 of period 2). All adverse events were mild in intensity.

	Nintedanib 150 mg alone	Nintedanib 150 mg coadministered with multiple doses of bosentan 125 mg bid	Adjusted geometric mean ratio (90% CI)
C_{max} (ng/mL)	21.9	22.7	103.4 (86.1, 124.0)
AUC_{0-tz} (ng·h/mL)	194.9	192.6	98.9 (91.3, 107.0)
$AUC_{0-\infty}$ (ng·h/mL)	204.3	208.3	102.0 (94.9, 109.6)

Conclusions: Coadministration of bosentan 125 mg bid had no effect on the pharmacokinetics of a single dose of nintedanib 150 mg.