sidering the interstitial lung disease (ILD) status of the SSc patients (determined using HRCT). For this phenotype-specific analysis, Immunochip genotype data were available for 589 ILD+ SSc patients and 1,333 ILD- SSc patients from 4 European cohorts.
Pooled analysis of the discovery populations with the replication cohorts was performed using the inverse variance method under a fixed effects model. Significance threshold was established at the genome-wide level (p<5x10-8).
Results. We identified a model comprising 6 polymorphic amino acidic positions and 7 SNPs that explained the observed significant associations in the HLA region. Moreover, we identified 3 novel SSc risk loci showing genome-wide level associations. These novel loci included: DNASE1L3, SCHIP1 | IL12A and ATG5. Remarkably, the association of the rs35677470 functional missense variant in the DNASE1L3 locus with the ACA+ subset of patients is the most significant non-HLA association with SSc revealed to date (p=2.70x10-32 OR=2.00). In addition, we further refined the area of association for the STAT4, IRF5/TNPO3 loci and related an observed peak of association in the PXK gene to the novel DNASE1L3 locus. Seven SNPs showed suggestive p-values in the ILD+ versus ILD- patient analysis and a replication step comprising 497 ILD+ and 853 ILD- patients is in progress.
Conclusions. This study provided a comprehensive insight into the association of the HLA region with SSc, identified 3 new SSc susceptibility loci and proposed new candidates for SSc-related ILD.

Session 12: *Pulmonary Arterial Hypertension*

S.12.1

PAH: HOW TO MAKE THE RIGHT DIAGNOSIS AT THE RIGHT TIME

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With the availability of effective targeted therapies for pulmonary arterial hypertension associated with systemic sclerosis (SSc-PAH), the detection of early stages of SSc-PAH has become a major task for the treating physicians. The most frequent diagnostic measures used in clinical practice to detect suspected PAH are lung function tests with DLCO and transthoracic echocardiography. However, while in advanced stages echocardiography might be a useful tool to suspect PAH, accumulating data show that standard echocardiography as a single measure is insufficient to detect PAH in early or even preclinical stages. These findings have let to different initiatives trying to establish recommendations and screening algorithms for the early detection of SSc-PAH. Recommendations were based on different consensus methods such as Delphi exercises and the RAND/University of California, Los Angeles consensus methodology. Evidence-based data were derived from multicenter studies with multivariate regression analysis and resulted in prediction scores such as the DETECT-score for PAH and the Cochin Risk prediction score for PH. These and other recommendations and prediction scores will be presented and their use in clinical practice will be discussed in this presentation. Most importantly, right heart catheterization remains the gold standard for the diagnosis of PAH

S.12.2

CHARACTERISTICS OF SYSTEMIC SCLEROSIS PATIENTS WITH PULMONARY HYPERTENSION AND A PULMONARY CAPILLARY WEDGE PRESSURE >15 IN THE PHAROS REGISTRY

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Background. Systemic sclerosis (SSc) commonly leads to pulmonary hypertension (PH), which may be associated with left heart disease and an elevated pulmonary capillary wedge pressure (PCWP). Patients in this PH subgroup may have mean pulmonary artery pressures (mPAP) in proportion to their elevated PCWP (pulmonary venous hypertension, "PVH") or higher than expected given their PCWP ("out-of-proportion PH"). It is not known what causes this difference in patients with SSc.
Methods. Baseline characteristics from 48 patients in the PHAROS registry who had a PCWP>15 on right heart catheterization (RHC) were retrospectively analyzed. Characteristics of those who died before 2 years of follow-up (n=10) were compared to those who were alive at 2 years (n=20). Patients were divided into 2 groups based on their initial RHC diastolic pressure gradient (DPG=diastolic PAP minus PCWP): PVH (DPG<5mmHg) or out-of-proportion PH (DPG>5mmHg). Comparisons were made between groups using unpaired t-tests or Chi square. Kaplan-Meier analysis compared survival and time to first hospitalization.
Results. At baseline, the mPAP was 36.8±11.8 mmHg and the PCWP was 19.4±3.3mmHg. Univariate factors associated with death prior to 2 years are shown in the table. In multivariate analysis, the only independent factors associated with death prior to 2 years were lower 6MWD (p=0.01) and higher PCWP (p=0.01). The out-of-proportion PH group (n=26) had higher baseline mPAP (42.7±13.0 vs. 29.7±3.7mmHg, p<0.0001), DPG (12.7±8.6 vs. 2.9±1.5mmHg, p<0.0001), and pulmonary vascular resistance (376±235 vs. 204±101 dynes/sec/cm5, p=0.003) compared to the PVH group (n=22). Although there was no difference in baseline immunosuppression use overall, mycophenolate (MMF) use was less common in the out-of-proportion PH group (8% vs. 37%, OR 0.15, p=0.027). There were no differences between the PVH and the out-of-proportion PH groups in age, sex, disease duration, pulmonary function, SSc subtype, or 6MWD (all p>0.05). There was no difference in 3-year survival between the 2 subgroups (PVH: 1-year=95%, 3-year=61%; out-of-proportion PH: 1-year=85%, 3-year=63%, p=0.73). There was a trend towards shorter time to first hospitalization in the out-of-proportion PH group (p=0.13).
Conclusion. In patients with SSc-PH and a PCWP>15, lower 6MWD and higher PCWP were independently associated with an increased risk for death within 2

years. In SSc patients with a PCWP>15, those with out-of-proportion PH were less likely to be on MMF compared to those with PVH. The relationship between MMF and PH in SSc needs further investigation, as MMF's anti-fibrotic effects may theoretically decrease pulmonary artery remodeling in these patients.

Table. Baseline characteristics in patients dying prior to 2 years of follow up compared to those who survived for more than 2 years.

Parameter	Death within 2 years	Survival >2 years	*p*-value
Age (years)	58.3±15.5	54.1±12.3	0.68
Sex (% female)	56%	85%	0.16
SSc disease duration (years)	8.9±6.8	8.2±8.4	0.83
Scleroderma type (%)			
Limited	40%	55%	0.71
Diffuse	50%	35%	
NYHA functional class			
I/II	30%	73%	0.05
III/IV	70%	27%	
Immunosuppressant use at baseline (% yes)	20%	44%	0.40
6-minute walk distance (meters)	186±96	366±107	0.002
Borg Dyspnea Score	5.7±3.2	2.7±2.0	0.03
Mean pulmonary artery pressure (mmHg)	40.0±9.8	32.7±9.1	0.05
Pulmonary capillary wedge pressure (mmHg)	22.9±4.3	18.6±2.4	0.001

S.12.3

RECOMMENDATIONS FOR SCREENING AND DETECTION OF CONNECTIVE-TISSUE DISEASE ASSOCIATED PULMONARY ARTERIAL HYPERTENSION

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Background. Pulmonary arterial hypertension (PAH) affects up to 15% of patients with connective tissue diseases (CTD) and is one of the leading causes of mortality in systemic sclerosis (SSc) and mixed connective tissue disease (MCTD). Previous recommendations were developed as part of larger efforts in PAH and did not provide detailed recommendations in CTD-PAH.
Objectives. To develop recommendations for screening and early detection of CTD-PAH using rigorous data-driven and consensus-building methodology.
Methods. We performed a systematic review for the screening and diagnosis of PAH in CTD by searching available databases. Using the RAND/UCLA methodology, we developed case scenarios followed by 2 stages of voting—first one was voted anonymously by 10 international experts on 1 (inappropriate) -9 (appropriate) scale and 2nd voting after face-to-face meeting.
Results. The key recommendations include:

Recommendations for RHC for SSc and scleroderma-spectrum disorders.

Non-invasive test	Threshold for RHC	Signs or symptoms* required for RHC
TTE	TR velocity of 2.6-2.8 m/s	Yes
	TR velocity of >2.8 m/s	No
	Right atrial (RA maior dimension >53mm) or righ ventricular enlargement (Mid cavity RV dimension >35mm), irrespective of TR velocity	No
FFTs	FVC/DLCO ratio >1.6 &/or DLCO <60%**	Yes
	FVC/DLCO ratio >1.6 &/or DLCO<80% & NT-Pro BNP >2 times upper limit of normal**	
Composite measure	Meets DETECT algorithm in patients with DLCO<O0% & disease duration >3 years	No

*Symptoms: dyspnea on rest or exercise, fatigue, pre-syncope/ syncope, chest pain, palpitazions, dizziness, lightheadedness. Signs: Loud pulmonic sound, peripheral edema. **TTE without overt systolic dysfunction, greater than grado I diastolic dysfunction or greater than mild mitral or aortic valve disease or evidence of PH.

1. All patients with SSc should be screened for PAH.
2. MCTD or other CTD's with scleroderma features (referred hereon as scleroderma-spectrum disorders) should be screened similar to patients with SSc.
3. Screening of asymptomatic patients is not recommended for MCTD or other CTD patients without features of scleroderma.
4. RHC is mandatory for diagnosis of PAH.
5. Acute vasodilator testing is not required as part of the evaluation of PAH in patients with SSc, SSc-spectrum disorders, or other CTDs.
6. Initial screening evaluation in patients with SSc and scleroderma-spectrum disorders include pulmonary function test (PFT) including diffusion capacity carbon monoxide (DLCO), Transthoracic echocardiogram (TTE), NT- Pro BNP, and DETECT algorithm if DLCO% <60% and >3 years disease duration.
7. In SSc and SSc-spectrum disorders, TTE and PFT should be performed on an annual basis or TTE, PFT, and NT-Pro BNP if new signs or symptoms develop.
Conclusions. We provide consensus-based and evidence-driven recommendations for screening and early detection of CTD-PAH. It is our hope that these recommendations will lead to early detection of CTD-PAH and ultimately improve patient outcomes.

S.12.4

A COMPARISON OF THE PREDICTIVE ACCURACY OF THREE SCREENING MODELS (DETECT V.ESC/ERS V. ASIG) FOR PULMONARY ARTERIAL HYPERTENSION IN SYSTEMIC SCLEROSIS

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Background and Aim. There is evidence that screening for Pulmonary Arterial Hypertension (PAH) in systemic sclerosis (SSc) improves outcomes. We compared the predictive accuracy of two recently published SSc-PAH screening algorithms (DETECT 2013 and Australian Scleroderma Interest Group - ASIG 2012) with the commonly used European Society of Cardiology / Respiratory Society (ESC/ERS 2009) guidelines.
Method. We included 71 consecutive SSc patients with suspected PAH undergoing RHC. We excluded patients with FVC<40%. The three screening models were applied to each patient as follows: a positive screen in DETECT was a score of 300+ in 'step 1' (FVC/DLCO%, telangiectasia, anti-centromere antibody, NT-proBNP, urate, ECG right axis deviation) together with a score of 35+ in 'step 2' (step 1 points, RA area, tricuspid regurgitant velocity [TRV]) calculated using a nomogram; a positive screen in the ASIG algorithm was DLCOCORR <70% and FVC/DLCOCORR>=1.8, or NT-proBNP>=210 pg/ml; a positive screen in the ESC/ERS guidelines was TRV >3.4 m/s, or TRV >2.8-<=3.4 and symptoms, or TRV <=2.8 m/s and symptoms and additional suggestive echo variables. PAH was defined as mPAP>25 and PCWP<=15 mmHg on RHC. For each model, contingency table analysis was used to determine sensitivity, specificity, positive (PPV) and negative predictive values (NPV) for PAH. These test properties were also evaluated in an 'alternate scenario analysis' where the prevalence of PAH was set at 10%.
Results. RHC revealed PAH in 27 (38%) patients, while 10 patients had WHO group 2 and 3 PH and were excluded from further analyses. TR jet was undetectable in 3 patients to whom the ESC/ERS guidelines could not be applied; none had PAH on RHC. Test properties of the three models are summarized in Table I. Both DETECT and ASIG algorithms performed equally well with sensitivity and NPV of 100%. However, the ESC/ERS guidelines had NPV of only 90%, missing one case of PAH. All three models lacked specificity, ranging from 29% to 47.1%. With PAH prevalence set at 10%, the NPV of the models was unchanged, but the PPV dropped (Table I).
Conclusion. In this cohort, the DETECT and ASIG algorithms out-perform the ESC/ERS guidelines, detecting all patients with PAH. The specificity of all models is low, as may be expected in a screening test. The ESC/ERS guidelines have limitations in the absence of a TR jet. Ultimately, the choice of SSc-PAH screening algorithm will depend on cost and ease of application.

Table I. Comparison of the performance of DETECT v. ESC/ERS v. ASIG screening models for SSc-PAH.

				PAH prevalence set at 10%		
	Detect n=61	Esc/Ers n=58	Asig n=61	Detect n=61	Esc/Ers n=58	Asig n=61
Sensitivity (95%CI)	100% (87.2-100)	96.3% (81-99.9)	100% (87.2-100)	100% (54.1-100)	96.3% (54.1-100)	100% (54.1-100)
Specificity (95v CI)	35.3% (19.7-53.5)	29.0% (19.7-53.5)	47.1% (29.8-64.9)	35.3% (23.8-50.4)	29.0% (12.5-36.8)	47.1% (35.4-62.9)
PPV (95% CI)	55.1% (40.2-69.3)	54.2% (39.2-68.6)	60% (44.3-74.3)	14.7% (5.6-29.2)	13.1% (4.9-26.3)	17.4% (6.8-34.5)
NPV (95% CI)	100% (63.1-100)	90.0% (55.5-99.7)	100% (79.4-100)	100% (83.2-100)	99.7% (73.5-100)	100% (87.2-100)

S.12.5

CLINICAL SUBTYPE AND AUTOANTIBODIES BOTH HELP PREDICT PULMONARY ARTERIAL HYPERTENSION, BUT AUTOANTIBODIES ARE STRONGER PREDICTORS OF DEVELOPING SECONDARY PULMONARY HYPERTENSION

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Purpose. Our objective was to assess whether clinical subtype (limited versus diffuse skin) or antibody is a stronger predictor of pulmonary hypertension (PH) development.
Methods. From our prospectively enrolled institutional SSc databank we performed a cross-sectional study of SSc patients seen between 1.1.2000 and 31.12.2009. PH was defined as a mean pulmonary artery pressure (PAP) > 25 mmHg on right heart catheterization (RHC) or echocardiogram with PAP > 45 and diagnosed by a cardiologist. PH was classified as pulmonary arterial hypertension (PAH), or "secondary" PH from heart (PH-heart) or interstitial lung disease (PH-ILD). Patients with PH not related to SSc were excluded. Antibody testing was performed for nine SSc-antibodies by immunofluorescence, immunodiffusion and immunoprecipitation. Separate logistic regression models were created to perofrmed whether antibody or clinical subtype were predictors of PAH and secondary-PH (PH-heart + PH-ILD). To answer this targeted question age at initial visit, gender, clinic subtype and antibody were included in the models using a cut-off of $p<0.10$. Interactions were assessed.
Results. 13 patients were excluded. Of the 1,152 SSc patients included, 80% were female, 91% Caucasian, the mean age at first visit was 51±13 years, and 56% had limited SSc. 97% had complete antibody testing. 197 (17%) had PH. There were 113 (10%) with PAH, 23 (2%) with PH-heart and 61(5%) with PH-ILD. 81% were RHC confirmed. Antibody distribution was 20% anti-centromere (ACA), 18% anti-Scl70, 24% anti-RNA polymerase III, 6% anti-U1RNP, 8% anti-Th/To, 4% anti-PM/Scl, 3% anti-U3RNP, 2% anti-U11/U12 RNP, 1% anti-Ku and 11% with other antibodies on immunoprecipitation.
The final model for PAH is shown in Table I and for secondary-PH in Table II. As testing for Th/To and U3RNP are not readily available, and these are grouped in published literature as a "positive nucleolar ANA", they were combined. On final multivariable analysis age, limited skin, and Th/To or U3RNP (positive nucleolar ANA) were predictors of PAH, with clinical subtype and these antibodies having similar odds ratios.
For secondary-PH increasing age, male gender, and anti-U11/12 positivity increased the risk, while ACA-positivity decreased the risk. Limited skin disease was a weaker predictor for secondary-PH, and was excluded from the multivariable model when stricter criteria ($p<0.05$) were used.
Conclusions. Both clinical subtype and Th/To or U3RNP antibodies are important, nearly equivalent predictors of PAH. However, age, gender and antibodies were clearly stronger predictors of risk for developing secondary-PH then clinical subtype.

Table I. Multivariable Predictors of PAH.

		Odds Ratio (95% Confidence Interval)	*p*-value
Age (years) at initial visit			<0.0001
	<35	–	
	35-44	0.83 (0.37-2.10)	
	45-54	1.07 (0.48-2.42)	
	55-64	2.11 (0.94-4.73)	
	>65	3.54 (1.64-8.07)	
Limited cutaneous involvement		2.74 (1.67-4.48)	<0.0001
Th/To or U3RNP positive (nucleolar ANA)		2.66 (1.61-4.41)	<0.0001

Table II. Multivariable Predictors of Secondary PH.

		Odds Ratio (95% Confidence Interval)	*p*-value
Age (years) at initial visit		0.03	
	<35	–	
	35-44	1.23 (0.43-3.59)	
	45-54	1.95 (0.72-5.29)	
	55-64	2.70 (0.98-7.43)	
	>65	3.53 (1.25-9.97)	
Male		2.18 (1.32-3.59	<0.002
Anti-U11/U12 RNP positive		1.51 (0.93-2.45)	0.02
ACA		0.27 (0.11-0.67)	0.004
Limited cutaneous involvement		3.12 (1.17-8.34)	0.09

S.12.6

PROGNOSTIC VALUE OF NT-PROBNP IN SYSTEMIC SCLEROSIS PATIENTS WITHOUT PULMONARY HYPERTENSION

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Background. NT-proBNP has a recognized role as a diagnostic and prognostic marker in systemic sclerosis (SSc)-associated pulmonary arterial hypertension (PAH) (1). However, NT-proBNP levels are known to increase in a number of pathologic conditions potentially affecting the prognosis SSc patients (2).
Aim of the Study. to assess the prognostic value of raised NT-proBNP in SSc patients without PAH.
Materials and Methods. 92 (88 F 4 M) SSc patients (limited 78, diffuse 14) were analyzed. Patients with right heart cath-confirmed PAH, severe valvular heart disease or LV systolic disfunction (EF <55%) were excluded from the study, with inclusion of patients with borderline PAPs at cardiac echo but cath mean pulmonary arterial pressure <25 mmHg. The patients were divided in two groups according to NT-proBNP levels <=400 pg/mL (BNP-L, N=74) or >400 pg/mL (BNP-H, N=18). Baseline variables were compared by analysis of variance or chi-square statistics. Survival analysis was performed by Cox proportional- hazard regression.
Results. Mean age at entry was 57.58±13.27 yrs. Mean echo pulmonary arterial pressure was 30.55±7.66 mmHg. Average NT-proBNP levels were 261.63 pg/mL (range 5 – 3129). Mean age (67.7±8.75 vs. 55.12±13.06, $p=0.000$), PAPs (36.86±5.91 vs. 28.91±6.47, $p=0.000$), the prevalence of diffuse SSc (33.3% vs 10.8%, $p=0.027$), clinically significant interstitial lung involvement (55.6% vs. 20.3%, $p=0.006$), mRSS (13.71±11.47 vs 4.50±6.23) and the percentage of patients with active digital ulcers (50.0% vs. 18.9%, $p=0.010$) were significantly higher in BNP-H patients. BNP-H patients had lower mean DLCO (61.30±19.58 vs 76.17±18.63, $p=0.025$), walked a significantly shorter distance at 6MWT (259.45±142.11 vs. 368.15±107.58, $p=0.005$), and showed lower mean hemoglobin levels (11.78±1.29 vs 12.75±1.30, $p=0.007$). Mean serum creatinine and VAS scores (RP, Dyspnea, GI involvement) were not different between the 2 groups ($p>0.05$). During follow-up (mean FU time 7.50±2.49 yrs) 12 patients died, 8 in the BNP-H group and 4 in the BNP-L group. In Cox analysis, only NT-proBNP levels and ILD presence were included in the regression model. Survival probability was significantly lower in BNP-H patients ($p=0.0025$).

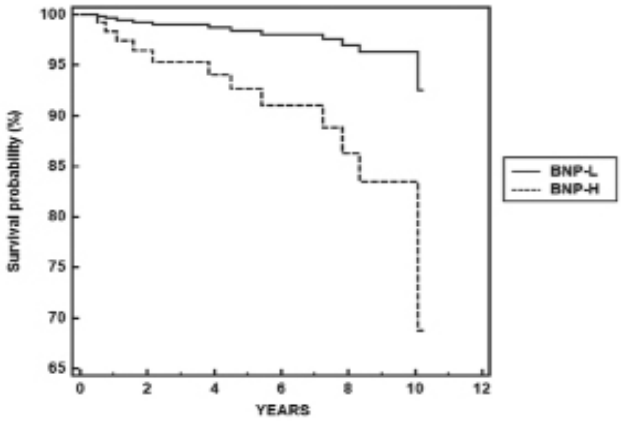

Fig. 1. Survival probability in BNP-L and BNP-H patients (Cox regression).

Conclusion. high levels of NT-proBNP are associated with increased mortality in SSc patients even in the absence of overt pulmonary arterial hypertension. Our findings lend further support to the inclusion of NT-proBNP dosage in the periodic screening algorithms of SSc patients.

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Special Lecture

SL.1.1

DESSCIPHER, A JUMP IN THE FUTURE

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DeSScipher aims at improving clinical practice in the management of SSc for which no orphan drug is available. Over a three-year period, building upon the expertise of a multidisciplinary experienced consortium combining clinicians, physicians, biostatisticians, biologists and chemists, DeSScipher will provide a systemic approach to SSc. This approach isbased on five observational trials including different dimensions of the SSc disease: from early detection to severe complications, from child to adult patients, different organ levels (lung, heart) and integrates all generated outputs at the complexe level of the SSc disease. This project is comparing the outcomes of different preventive measures and treatments in terms of efficacy of off-label drugs and of adverse events from the early phase to severe phases of the SSc-associated diseases. DeSScipher will define appropriate outcome measures (OM) in SSc management. It includes several key experts - experienced in working together - from the EUSTAR consortium with more than 150 expert centres and 9000 well controlled and documented patients. Consequently, it is the aim of the DeSScipher project to improve clinical practice in the management of SScoccuring in adults but also in children by relying on the activities of the EUSTAR consortium. The concept of DeSScipher is using the EUSTAR long-term databank MEDSonline (Minimal Essential Data Set), the EUSTAR biobank and a preliminary diagnostic tool VEDOSS and to analyse and extend these data to shed light on specific molecular, genetic and functional details of SSc pathophysiology ranging from the early inflammatory phase to alterations of the vascular architecture to the clinically overt fibrosis of the connective tissues of the skin and internal organs. To facilitate the approach of DeSScipher, five observational trials are running to cover the disease evolution phases from early diagnosis such as digital ulcers and hand arthritis to the associated morbidity-driving pathologies such as interstitial lung disease, pulmonary hypertension or left heart disease. For this purpose, DeSScipher compares different scenarios: preventative measures and/or treatments to define appropriate primary and secondary outcome measures in order to evaluate the effectiveness as well as the adverse effects of the off-label candidate drugs and orphan drugs. For that purpose, the MEDSonline database as the biggest database in the field of an orphan rheumatic disease and the EUSTAR biobank have also been made available for and implemented by DeSScipher. DeSScipher will also serve as prototype approach for all other orphan diseases in the field of rheumatology and clinical immunology with similar problems in recruiting and documenting patients for testing novel drugs and establishing validated general international recommendations. Interested to contribute ? Visit the booth at the 3rd WSC or our website www.desscipher.eu or mail desscipher@med.uni-giessen.de
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