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Table 2. Risk factors for cardiovascular mortality (MCV)

	Bivariate		Multivariate	
	HR (IC 95%)	p	HR (IC 95%)	p
Sex		0.2		0.1
Arrhythmia	3.8 (1.6-9.2)	0.003	3.4 (1.4-8.4)	0.007
Number of therapies	0.6 (0.4-0.9)	0.03	0.5 (0.3-0.9)	0.01
GC withdrawal due to IM remission		0.2	0.4 (0.1-1.005)	0.05

AB0207

RECEPTOR EXPRESSION OF ANGIOTENSIN TYPE-1 AND 2 ARE DECREASED IN PATIENTS WITH SYSTEMIC SCLEROSIS AND PULMONARY ARTERIAL HYPERTENSION (PAH) AND CORRELATED WITH SEROLOGICAL LEVELS OF NT-PROBNP

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Background: Previous studies identified functional autoantibodies against the angiotensin receptor type-1 (AT1R) and the endothelin receptor type A (ETAR) in about 85% of the patients with systemic sclerosis (SSc, 1). The antibodies are cross-reactive, agonistic and functionally active by increasing the effects of the natural ligands as well as by specific activation of the receptors (2, 3). The levels of the antibodies are associated with clinical findings such as pulmonary arterial hypertension (PAH). Patients with highest antibody levels show worst prognosis and do not respond well to receptor blocker therapy (2-4). Several in vitro effects of the antibodies depend on the antibody levels and on the cell type bearing the receptors. Receptor expression of ETAR and AT1R was highest in early disease (3).

Objectives: To determine predictors of PAH, DU and clinical complications by measuring the antibody levels and the receptor expression on peripheral mononuclear cells in patients with systemic sclerosis.

Methods: The current study analyzed the serological levels of anti-AT1R and anti-ETAR antibodies and the extracellular and intracellular expression of AT1R, AT2R, ETAR and ETBR on circulating CD4pos T cells, CD8pos T cells, CD14pos Macrophages, CD15pos Granulocytes and CD19pos B cells in SSc (n=41) using sandwich ELISA and flow cytometry. Clinical data (PAH, history of digital ulcers, digital-ulcers score, mRSS, pulmonary fibrosis, therapy) and serological markers (ESR, CRP, NT-proBNP) were gathered at the time of serum sampling and every three-month up to 27month after baseline.

Results: Patients with PAH demonstrated a lower AT1R MFI and AT1R/AT2R MFI ratio on all PBMC. Levels of NT-proBNP correlated negatively with the AT1R MFI and AT1R/AT2R MFI ratio on all PBMC. The levels of anti-AT1R ab correlated with the NT-proBNP in SSc patients with levels of NT-proBNP <300pg/ml. AT1R MFI on T cells, Granulocytes and Macrophages distinguished between pathological and physiological levels of NT-proBNP. Using Log-rank test and Mantel-Cox proportional hazards model, decreased expression of AT1R MFI on T cells, Granulocytes and Macrophages identified trends of deterioration of NT-proBNP over 50%.

Conclusion: Expression of AT1R and AT2R on PBMC could be of diagnostic value identifying clinical progress and/or subgroups in SSc. Their role in the pathophysiology, e.g. their impact of endothelial damage, has to be further investigated in SSc.

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AB0208

UP-REGULATION OF TMEM176A AND TMEM176B IN PERIPHERAL BLOOD CELLS, A POSSIBLE BIOMARKER FOR THE DEVELOPMENT OF EARLY PULMONARY VASCULAR DISEASE IN SYSTEMIC SCLEROSIS

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Background: Pulmonary arterial hypertension (PAH) is prominent as a vascular involvement of systemic sclerosis (SSc), which remains a leading cause of death in spite of current best treatments. As the pulmonary vascular disease (PVD) can be well compensated for, more than 2/3 of the pulmonary circulation is impaired by the time of diagnosis. However, there were few studies focusing on the molecular mechanisms of PVD at the subclinical stage of PAH in SSc patients.

Objectives: To detect candidate genes involved in the development of PVD before diagnosis of PAH in SSc patients.

Methods: Total of 88 patients who had not met PAH criteria with Raynaud phenomenon (n=75), skin sclerosis (n=58) or SSc-related autoantibody (n=59) was enrolled. To detect the early PVD, exercise Doppler echocardiography (exDE) was carried out. The exercise induced pulmonary arterial hypertension (exPAH) group was segregated from normal response group (exN) with using the reported definition¹). The exDE was followed every 6 or 12 months for up to 3 years. For gene expression analysis, total RNAs from whole peripheral blood cells were extracted by PAXgene system and multiplex sequencing was done. To identify candidate genes involved in the pathogenesis of the early PVD, the differentially expressed genes (DEGs) between exPAH and exN group were visualized by volcano plots, a scatter plots calculated to show fold-changes and p-values of DEGs. After identifying the candidate genes, weighted gene co-expression network analysis (WGCNA) was performed to find the co-expressed gene cluster. And then, enrichment analysis using gene ontology (GO) terms were performed to investigate roles of the gene cluster in pathogenesis of PVD.

Results: Patients were fall into exPAH group (n=14) and exN group (n=74) at the baseline. After gene expression analysis, 1204 DEGs between exPAH and exN group were identified. Volcano plots indicated that expressions of TMEM176A and TMEM176B were prominent (log₂ fold-change >1.25 and -log₁₀p-value >3.5) in exPAH patients. We also found that the expressions of these genes were highly correlated with each other (R²=0.9724, p<0.01). 11 out of 74 patients (14.9%) in exN group progressed to exPAH group during follow-up period (24.8±11.3 months). The expressions of TMEM176A/B at the baseline were significantly up-regulated in the group of clinical progression as compare with others (log₂ fold-change from the average: TMEM176A: 0.78±1.31 vs. -0.35±1.65; p=0.022, TMEM176B: 0.71±1.38 vs. -0.38±1.78; p=0.034). By WGCNA and GO enrichment analysis, the terms, such as related to "apoptosis", "Toll-like receptor signaling" and "dendritic cell differentiation" were found in the co-expressed gene cluster of TMEM176A/B.

Conclusion: Although elucidating the mechanisms for progression of early PVD in SSc remains a major challenge, (1) we found up-regulation of TMEM176A/B was prominent in exPAH group; (2) TMEM176A/B was significantly up-regulated at the baseline in the patients progressed from exN to exPAH group during the follow-up period; (3) the co-expressed gene cluster of TMEM176A/B includes genes related to "apoptosis", "Toll-like receptor signaling" and "dendritic cell differentiation". TMEM176A/B was found initially to be a regulator for DC maturation in mice²) but functions of human ortholog of these genes remain still unclear. However, our findings suggest that the up-regulation of TMEM176A/B in peripheral blood cells is possible to be a biomarker for the development of early PVD in SSc.

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