Differentiation of ATTR and AL amyloidosis based on abdominothoracic organ-specific uptake of ^{124}I-AT-01 (^{124}I-p5+14) assessed by PET/CT imaging

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BACKGROUND: Cardiac amyloidosis is a common clinical feature of both transthyretin (ATTR) and monoclonal immunoglobulin light chain (AL) associated amyloidosis. At present there are no approved methods for imaging amyloid deposits in the heart or other abdominothoracic organs. In addition to diagnosis, imaging amyloid distribution and organ load, and monitoring response to therapy, there would be clinical value if the imaging agent could, with acceptable specificity differentiate ATTR from AL amyloidosis.

Agents such as ^{99m}Tc-PyP and ^{18}F-florbetaben have demonstrated the potential to differentiate ATTR from AL amyloidosis based on selective uptake and differential washout kinetics, both related to the relative affinity of the reagent for the deposits (1, 2).

Herein, we present another method based on the relative organ uptake of ^{124}I-AT-01 (^{124}I-p5+14) seen by quantitative PET/CT imaging through an analysis performed on data collected in a Phase 1/2 study of the radiotracer in patients with amyloidosis, NCT03678259).

OBJECTIVE: The goal of this *post hoc* analysis was to investigate potential methods for differentiating patients with ATTR amyloidosis from those with AL amyloidosis by comparing quantitative uptake of ^{124}I-AT-01 in the heart, liver, spleen and kidney in PET/CT images. A cohort of patients with positive visual cardiac uptake of the radiotracer were included in the analysis (n=16 AL and n=17 ATTR).

METHODS: The ^{124}I-AT-01 study enrolled a total of n=57 subjects (>18 years of age). Forty-eight subjects (n=48) had systemic amyloidosis, two (n=2) subjects had localized AL amyloidosis, two (n=2) subjects were asymptomatic TTRv carriers, and a cohort of five healthy volunteers (n=5) were imaged. A total of 16 AL and 17 ATTR patients (n=33) had uptake of ^{124}I-AT-01 in the heart based on visual examination of the images by a nuclear medicine physician. The radioactivity in the heart, liver, spleen, kidney and blood pool (lumen of thoracic aorta) was quantified (Bq/cc) by manual region of interest analysis and a standard uptake value ratio (SUVR) for each organ determined using the blood pool as the reference tissue. The SUVR and heart SUVR-to-organ ratios from patients with ATTR or AL amyloidosis were assessed for statistical assumptions and then compared using two-tailed t-tests or Mann-Whitney U tests. Receiver operator characteristic (ROC) analyses were performed using the Wilson/Brown method (3). Significance was assumed at an α = 0.05.
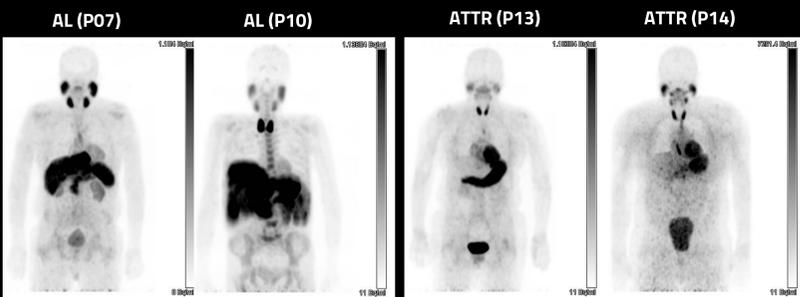

Figure 1. Characteristic biodistribution of ^{124}I-AT-01 in patients with AL and ATTR amyloidosis. Patients with AL amyloidosis generally have more than one organ involved, as compared to ATTR patients who generally have only cardiac uptake.
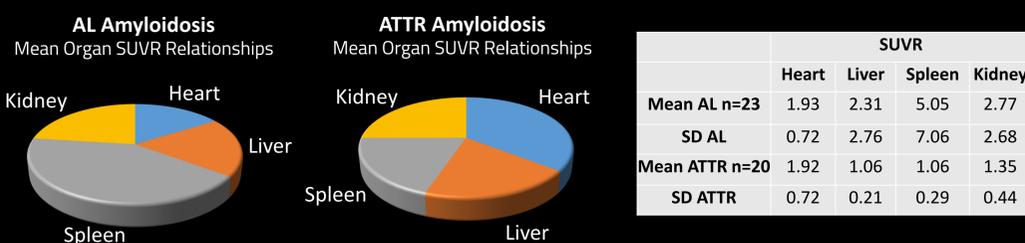

Figure 2. Distribution of mean standard uptake value ratios (SUVR) in patients with AL and ATTR amyloidosis. SUVR was calculated using the the blood pool as the reference tissue. In AL and ATTR patients the spleen and heart, respectively, have the highest SUVR.

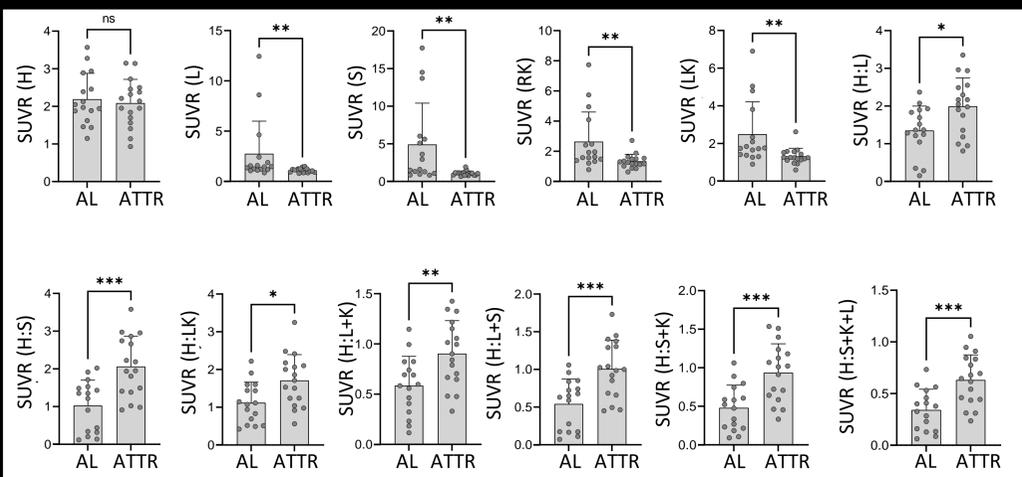|	SUVR			
	Heart	Liver	Spleen	Kidney
Mean AL n=23	1.93	2.31	5.05	2.77
SD AL	0.72	2.76	7.06	2.68
Mean ATTR n=20	1.92	1.06	1.06	1.35
SD ATTR	0.72	0.21	0.29	0.44

Figure 3. Comparison of standard uptake value ratios (SUVR) and organ ratios in patients with AL (n=16) and ATTR (n=17) amyloidosis and cardiac uptake of ^{124}I-AT-01. Except for the cardiac SUVR all organ- and organ ratio-based SUVR values were significantly different between AL and ATTR patients.
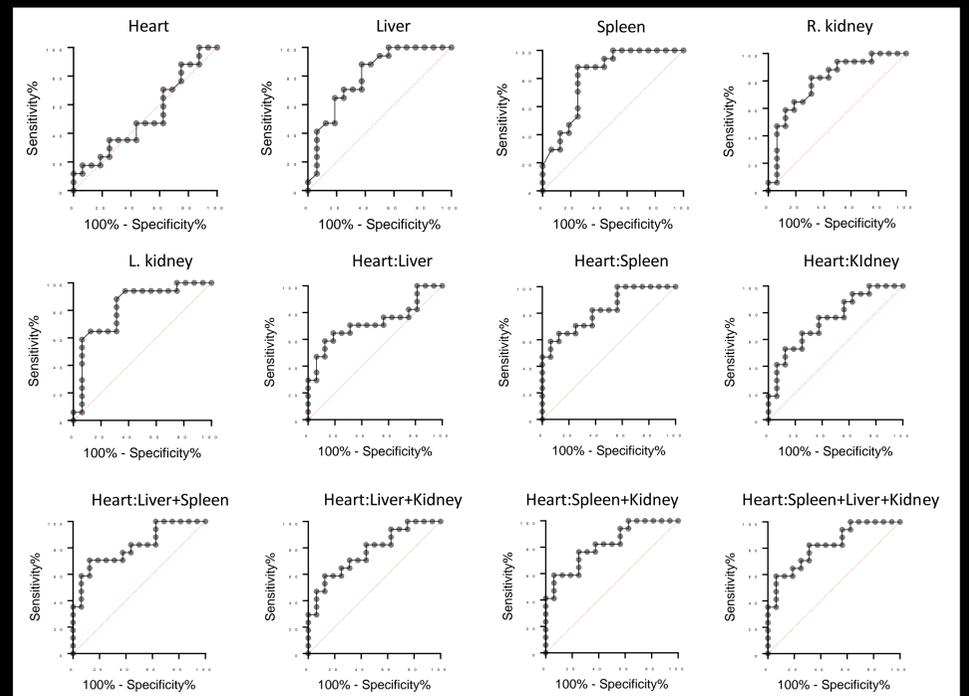

Figure 4. Evaluation of standard uptake value ratios (SUVR) and organ ratios in patients for the differentiation of ATTR from AL amyloidosis. Receiver operator curves comparing AL and ATTR parameters in patients with positive uptake of ^{124}I-AT-01 in the heart.

Test System	AUC	AUC (*p*-value)	AUC (95% CI)	Cut-off (SUVR)	Sensitivity %	Sensitivity 95% CI	Specificity %	Specificity 95% CI
H	0.52	0.810	0.32–0.73	-	-	-	-	-
L	0.80	0.003	0.65–0.95	<1.31	88.24	65.66-97.91	62.50	38.64-81.52
S	0.81	0.002	0.66–0.97	<1.28	88.24	65.66-97.91	75.50	50.50-89.82
RK	0.80	0.004	0.64–0.95	<1.56	82.35	58.97-93.81	68.75	44.40-85.84
LK	0.82	0.002	0.67–0.97	<1.62	88.24	65.66-97.91	68.75	44.40-85.84
H:L	0.72	0.028	0.55–0.93	>1.72	70.59	46.87-86.72	68.75	44.40-85.84
H:S	0.83	0.001	0.69–0.97	>1.37	82.35	58.97-93.81	36.64-81.52	
H:LK	0.75	0.014	0.58–0.92	>1.19	76.47	52.74-90.44	62.50	36.64-81.52
H:L+S	0.81	0.002	0.67–0.96	>0.68	76.47	52.74-90.44	62.50	36.64-81.52
H:S+LK	0.82	0.002	0.68–0.96	>0.58	82.35	58.97-93.81	62.50	36.64-81.52
H:L+LK	0.77	0.008	0.61–0.93	>0.70	70.59	46.87-86.72	68.75	44.40-85.84
H:S+L+LK	0.82	0.002	0.68–0.96	>0.42	82.35	58.97-93.81	68.75	44.40-85.84
H:(L+S+LK)/3	0.82	0.002	0.68–0.96	>1.27	82.35	58.97-93.81	68.75	44.40-85.84

Table 1. Parameters associated with the ROC valuation of standard uptake value ratios (SUVR) and organ ratios in patients for the differentiation of ATTR from AL amyloidosis. Parameters were generated from ROC analyses comparing AL and ATTR parameters in patients with positive uptake of ^{124}I-AT-01 in the heart.

RESULTS: There was significantly less amyloid (^{124}I-AT-01 retention) in the liver, spleen and kidney of patients with ATTR as compared to the non-ATTR cohort (p<0.005). Similarly, the heart-to-organ (heart:liver, heart:spleen, heart:kidney, heart:[liver+spleen], heart:[liver+kidney]) ratios were significantly lower in the non-ATTR patients (p<0.02) due to the larger denominator in these analyses. These data indicate that an ROC analysis could identify a cut-off value for discriminating ATTR amyloidosis. The area under the curve (AUC) values for all analyses were >0.7 and highly significant. Optimal cut-off values for discriminating ATTR patients were obtained using the spleen SUVR (AUC=0.81, p=0.002; 88% sensitivity and 76% specificity) and heart SUVR:spleen SUVR ratio (AUC=0.83, p=0.001; 82% sensitivity and 63% specificity).

SUMMARY: PET/CT imaging of patients with amyloidosis using ^{124}I-AT-01 allows for quantitative detection of pathology in major abdominothoracic organs. Analysis of radiotracer uptake in the heart, liver, spleen and kidney can be used to differentiate ATTR from non-ATTR forms of amyloidosis with high sensitivity and may provide additional insight on disease type following whole body PET/CT imaging with ^{124}I-AT-01. Additional studies will need to be conducted to refine and validate this potential additional utility of ^{124}I-AT-01 imaging

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