

Detection of extracardiac amyloid in patients with ATTR amyloidosis by PET/CT imaging using the amyloidophilic radiotracer ¹²⁴I-AT-01 (¹²⁴I-p5+14)

Jonathan Wall¹, Stephen J. Kennel¹, Alan Stuckey¹, Dustin Powell², Spencer Guthrie³, Emily Martin¹

¹University of Tennessee Graduate School of Medicine, USA. ²University of Tennessee Medical Center, USA. ³Attralus, Inc., USA

BACKGROUND: Transthyretin-associated (ATTR) amyloidosis is the most common form of systemic amyloidosis worldwide. Patients with ATTR amyloidosis are categorized by their dominant symptomology as either neuropathic or cardiomyopathic. This defines clinical management of the patient and the treatment options. Despite the classification into these two major pathologies, the anatomic distribution of ATTR amyloid deposits in the patient population can be extensive and heterogenous. This is supported by autopsy studies where numerous extracardiac and extraneuronal amyloid deposits have been identified (<https://doi.org/10.1016/j.prp.2021.153635>). However, due to the lack of amyloid-specific, whole-body, high-resolution imaging techniques, these deposits, and their clinical sequelae have not been fully appreciated in life. We have evaluated the ¹²⁴I-AT-01 PET/CT images from ATTR patients (*n*=20) who were enrolled in the Phase 1/2 imaging study (NCT03678259) for extracardiac uptake of radiotracer, indicative of the presence of amyloid.

OBJECTIVE: The goal of this analysis was to assess, by visual evaluation of ¹²⁴I-AT-01 PET/CT images, the uptake of radiotracer in extracardiac anatomic sites.

METHODS: The trial enrolled a total of *n*=57 subjects (>18 years of age) including patients with a diagnosis of ATTR amyloidosis (*n*=20). Both ATTRv (*n*=15) and ATTRwt (*n*=5) patients were recruited. All patients had a confirmed diagnosis of amyloidosis (based on biopsy, genotyping, or imaging studies). Subjects were administered a single IV dose of ¹²⁴I-AT-01 (<2 mCi I-124 and <2 mg AT-01). PET/CT images were acquired 5-6 h post injection using a low dose CT from crown to thighs. The images were reviewed by a radiologist who was blinded to the clinical status of the subject. Uptake of the radiotracer in organs and tissues was recorded. To assess the physiological distribution of radioactivity, a cohort of healthy subjects (*n*=5) were recruited and similarly evaluated.

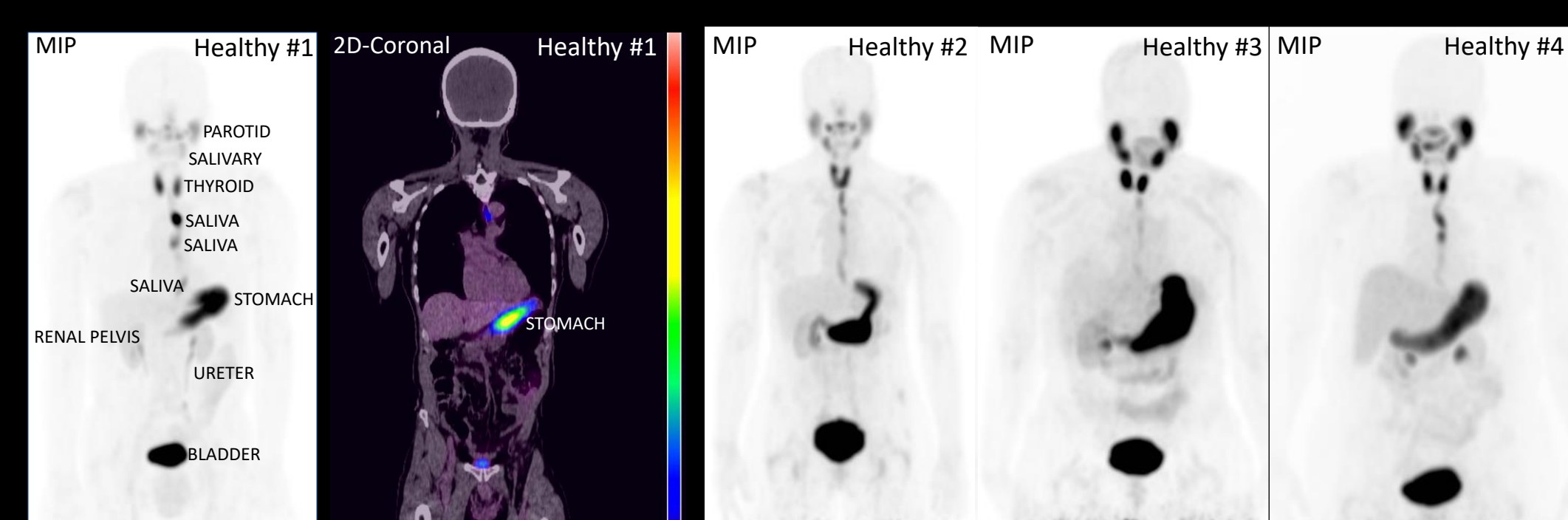


Figure 1. Biodistribution of radioactivity in healthy volunteers. ¹²⁴I-AT-01 is catabolized in the kidneys where some radioiodide is liberated. This then accumulates in stomach lumen, parotid, thyroid, and salivary glands, and the saliva. Other sites include, ureters, renal pelvis, and urinary bladder.

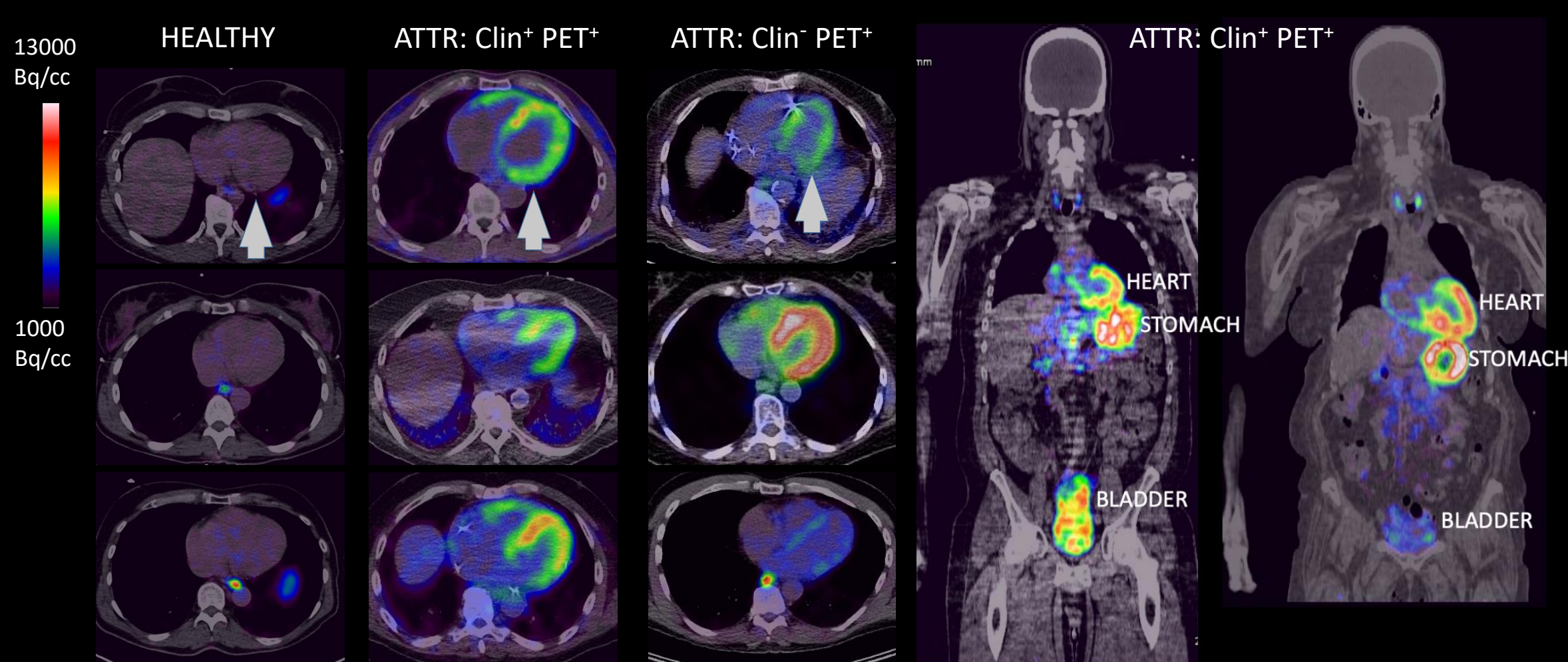


Figure 2. Specific cardiac uptake in patients with ATTR amyloidosis. In contrast to healthy volunteers, uptake of ¹²⁴I-AT-01 was seen in the left and right ventricular wall in patients with known cardiomyopathy (CM) and those without clinical imaging evidence of CM (Clin-).

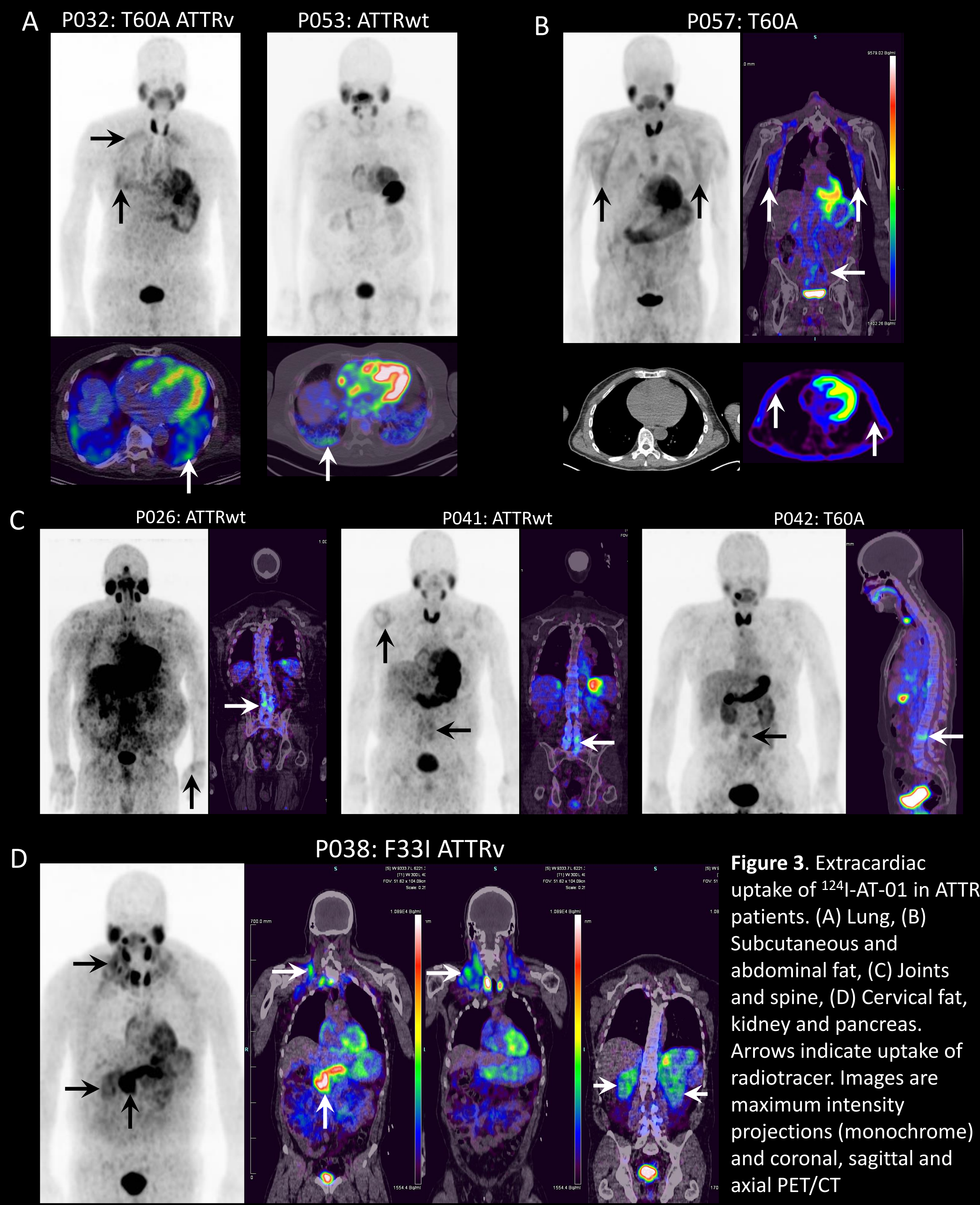


Figure 3. Extracardiac uptake of ¹²⁴I-AT-01 in ATTR patients. (A) Lung, (B) Subcutaneous and abdominal fat, (C) Joints and spine, (D) Cervical fat, kidney and pancreas. Arrows indicate uptake of radiotracer. Images are maximum intensity projections (monochrome) and coronal, sagittal and axial PET/CT

RESULTS: Uptake of ¹²⁴I-AT-01 was observed in at least one anatomic site in 19 ATTR patients (sensitivity = 0.95; 95% CI: 0.77, 1.00; *n*=20). Of the eleven (11/20) ATTR patients diagnosed with ATTR cardiomyopathy, cardiac uptake of ¹²⁴I-AT-01 was seen in all (sensitivity = 1.00; 95% CI: 0.74, 1.00; *n*=11).

Extracardiac uptake of ¹²⁴I-AT-01 in ATTR amyloidosis patients was observed principally in the: joints, including shoulders, spinal discs and facets (11/20); thoracic and lumbar spine (6/20); kidney (9/20); spleen (7/20); liver (5/20); and muscle (4/20). Additionally, uptake in other anatomic sites including the lung, pancreas, adrenal glands, and pituitary gland were also observed in the PET/CT images. For the entire ATTR cohort, a total of 17 non-cardiac organs or tissues were deemed positive by ¹²⁴I-AT-01 imaging (Table 1).

SUMMARY: Despite being clinically considered to impact either cardiac or peripheral nerve function ATTR amyloid is known to deposit in multiple anatomic sites; however, the extent of the deposition and the clinical importance of extracardiac amyloid has yet to be appreciated. Using PET/CT imaging of ¹²⁴I-AT-01, we have shown heterogeneous and often extensive ATTR amyloid deposits in numerous extracardiac sites, commonly the joints (55%), kidney (40%) and spine (30%). Notably, no biopsies of suspected anatomic sites of amyloid deposition were performed in this study. Despite the small cohort of patients in this study, these preliminary observations warrant further investigation to determine the prevalence and clinical importance of these diverse sites of deposition. Extracardiac ATTR amyloid deposits may impact quality of life and potentially addressed with anti-amyloid therapies.

This study was supported in part with services from the NHLBI, through the Science Moving TowArds Research Translation and Therapy (SMARTT) program. The authors acknowledge funding support from grant CHE1904577 (RRI) and contributions to the Amyloidosis and Cancer Therapeutics Gift Fund (including CMC/Gerdau, Knoxville)

Patient	Type	Joints	Muscle	Esophagus	Lung	Spine	Liver	Spleen	Kidney	Pancreas	Adrenal	Tongue	Soft palate	Pituitary	Fat
4	A101V		right intercostal and latissimus dorsi	Yes											
8	L58H	costovertebral		Yes	Yes										
13	T60A			Yes	Yes										
14	T60A			Yes											
21	T60A					L2 vertebral body/ osteophyte T8 posterior lamina						Yes			
25	L58H												Yes		
26	WT	uncovertebral in thoracic and lumbar spine					Yes	Yes	Yes						
29	P44S	acromioclavicular				L3-L4 disc uptake			Yes						
31	V30M	spinal facets, pelvis joints, hamstring insertions					Yes	Yes	Yes			Yes	soft palate and retropharynx	Yes	
32	T60A	spinal discs and facets			Yes		Yes	Yes	Yes	Yes					
34	WT	spinal facets				T12 vertebral marrow vertebral marrow			Yes				Yes		
35	L58H	glenohumoral, spinal discs and facets	gastrocnemius				Yes	Yes	Yes				Yes	Yes	
36	L58H	spinal facet joints							Yes			Yes			
38	F33I	spinal facets	gastrocnemius						Yes	Yes	Yes	Yes			cervical and thoracic
39	WT														
41	WT	shoulder, spinal facets, hips				L1-L2 disc	Yes	Yes	Yes		Yes				
42	T60A					L3-L4 intervertebral disc			Yes						
46	V122I, V30M		bilateral soleus, mild diffuse												
53	WT	bilateral glenohumoral													neck, chest, abdomen
57	T60A														2/20
Percent Occurrence	25% WT 5/20 WT	55% 11/20	20.0% 4/20	20.0% 4/20	15.0% 3/20	30% 6/20	25.0% 5/20	35.0% 7/20	45.0% 9/20	10.0% 2/20	10.0% 2/20	15.0% 3/20	20.0% 4/20	10.0% 2/20	10.00% 2/20

Table 1. Summary of extracardiac uptake in ATTR patients following visual evaluation of ¹²⁴I-AT-01 PET/CT images. Sites of non-physiological radiotracer uptake (when observed in more than one patient) were recorded following visual evaluation of the PET/CT images by a Nuclear Medicine physician who was blinded to the patient details.