SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2018; 35; 342-353 DOI: 10.36141/svdld.v35i4.7342

Quantitative interpretation of FDG PET for cardiac sarcoidosis reclassifies visually interpreted exams and potentially impacts downstream interventions

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Abstract. *Background:* FDG PET is used in cardiac sarcoidosis (CS) diagnosis and management, including decisions about initiation and titration of immunosuppression. However, optimal methods to identify sarcoidosis-related inflammation on these scans is unknown. Traditional interpretive methods for FDG PET rely on qualitative visual analysis, but quantitative techniques including standardized uptake values (SUVs) may be more specific. This study evaluated the diagnostic reclassification of FDG PET studies using quantitative versus qualitative analysis and evaluated the potential impact of reclassification on downstream management and events. *Methods:* Cardiac-focused FDG PET examinations performed for the evaluation of CS were analyzed, comparing results from the clinically reported visual analysis to quantitative re-analysis using left ventricular maximal SUV values (SUVmax). Net diagnostic reclassification index (NDI) was calculated and compared to admissions, deaths, ICD placements, immunosuppression initiation/escalation. Of 154 exams, 22 were reclassified from positive to negative using quantitative re-analysis whereas only 2 clinically reported negative exams were quantitatively reclassified to positive, leading to a NDI of -13.0%. In the quantitatively negative/clinically reported positive group, 11 patients had immunosuppression adjusted after 22 exams and 4 ICDs were placed. *Conclusions:* Quantitative re-analysis of FDG PET for CS led to an overall negative diagnostic reclassification from positive to negative. Studies that were clinically reported as positive by visual analysis but reclassified as negative by quantitative analysis had numerous medical interventions but few clinical events. The low event rate suggests the use of quantitative interpretation of FDG PET for CS may help in providing providers with a more targeted therapeutic framework. *(Sarcoidosis Vasc Diffuse Lung Dis 2018; 35: 342-353)*

Key words: FDG PET, cardiac sarcoidosis

Abbreviations:
Used in text or a table without defining the acronym:
ECG (electrocardiogram)
PET (positron emission tomography)

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Accepted after revision: 7 August 2018
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Defined on first use:
CS (cardiac sarcoidosis)
FDG PET (18F-fluorodeoxyglucose positron emission tomography)
LVBP (left ventricular blood pool)
SUV (standardized uptake value)

Introduction

Cardiac sarcoidosis (CS) diagnosis and management often relies on identifying the presence of in-

flammation associated with the disease. FDG PET is one imaging modality frequently used to help identify areas of inflammation caused by sarcoidosis (1). Management of CS can involve the use of immunosuppression for treatment of this inflammation as well as ICD placement (2). These interventions are performed in an effort to decrease inflammation reported on FDG PET and potentially prevent downstream clinical events including heart failure and arrhythmias and improve atrio-ventricular conduction. However, they may come at a cost of potentially dangerous immunosuppression toxicities and/or device complications.

There are various methods used to interpret FDG PET exams in clinical practice (1). Traditional visual analysis of cardiac FDG uptake is qualitative and relies on normalization of FDG image intensity to background, a method developed for myocardial perfusion imaging (3). However, normalization in hot-spot imaging such as with FDG is subject to over-sensitivity. In FDG PET for cardiac sarcoidosis, a minimal increase in myocardial signal above the blood pool background can appear falsely intense secondary to the normalization process. This can lead to studies being interpreted as positive when images are displayed using a normalized method. In addition, normalization precludes accurate comparison of treatment response, where the changes in the intensity of FDG uptake from immunosuppression treatment may be important but cannot be quantified when images are normalized (4).

Quantitative analysis of FDG PET/CT imaging includes various methods based on standardized uptake values (SUV) including SUVmax, SUVmean, CMA (cardiac metabolic activity), CMV (cardiac metabolic volume) and coefficient of variance (3,5-8). The role of these measures in improving diagnostic and therapeutic accuracy is not entirely understood.

The purpose of this study was to evaluate the potential reclassification of FDG PET for CS using quantitative re-analysis of images that were clinically reported using visual interpretation and to examine the potential impact of diagnostic reclassification based on this re-analysis on downstream management decisions and clinical events. Our hypothesis was that quantitative re-analysis would lead to an overall downward classification of the presence of inflammation from positive to negative.

Methods

Patient cohorts and definitions of cardiac sarcoidosis

The study cohort included single bed position, cardiac-centered FDG PET/CT examinations performed at Yale-New Haven Hospital from November 2013 to October 2015 (which predated our use of quantitative analysis of cardiac FDG PET imaging) for the evaluation of cardiac sarcoidosis following a high-fat/low-carbohydrate diet and prolonged fasting. Standard FDG doses (8-10mCi), incubation times (90 minutes), acquisition and reconstruction protocols were used.

Patients were included in the "cardiac sarcoidosis total" cohort if they fulfilled one of the following set of criteria: 1) Either the Japanese Ministry of Health and Welfare (JMHW) modified criteria (with the addition of abnormal FDG) (7) and/or the Heart Rhythm Society Criteria (HRS) (2) including the need for either histological and/or clinical diagnoses of extra-cardiac sarcoidosis, 2) In cases where extra-cardiac sarcoidosis was not defined, but the patient met other JMHW criterion, these patients were classified as having isolated cardiac sarcoidosis. Isolated CS was defined as such because of the inability to diagnose isolated CS by current guidelines (9). Thus, by including those who met JMHW criteria without extra-cardiac sarcoidosis, we sought to add to the repository of limited data on this under-recognized entity. Patients who did not meet JMHW/HRS criteria or isolated cardiac sarcoidosis criteria were defined as non-cardiac sarcoidosis patients (non-CS). The Yale University Human Subjects IRB approved this study.

FDG PET/CT Image Analysis: Clinical report and quantitative re-analysis

The clinical FDG PET exam interpretation performed at the time of the exam acquisition was abstracted and categorized as: 1) abnormal positive cardiac FDG uptake (focal or focal-on-diffuse), 2) negative FDG uptake, or 3) diffuse (non-specific) FDG uptake. As was the standard in our lab at the time, clinical interpretation performed by all readers for these exams used only a traditional nuclear cardiology display system (WLCQ), where image intensity is normalized to the maximum intensity

pixel for that exam and exams are displayed in a traditional nuclear cardiology format (short axis, vertical and horizontal long axis slices). Quantitative and/or hybrid imaging review were not used for the interpretation used in the clinical report. This clinical, visual-based interpretation was used for comparison to quantitative re-analysis, below.

All exam images were re-analyzed for the purposes of this study by two experienced readers (DS and EJM) using quantitative metrics for cardiac FDG uptake on a GE AW hybrid imaging workstation as previously described (7). The results of this quantitative re-analysis were not clinically reported. Multiple quantitative measures were evaluated (ie. CMV, CMA, SUVmax), and all were similar in their diagnostic performance (data not shown). Cardiac SUVmax was measured and exams with cardiac SUVmax greater than a 1.5-times left ventricular blood pool (LVBP) threshold were considered quantitatively positive (7). Examples of clinical report/quantitative re-analysis concordant positive exams, concordant negative, clinical report positive/quantitative re-analysis negative, and clinical report negative/quantitative re-analysis positive exams are shown in Figure 1. In 30 exams, low-intensity (<4.7 g/ml, average = 2.6 g/ml) SUVmax was located near pacemaker/intracardiac device leads (confirmed as artifact from non-attenuation corrected images), the left coronary cusp of the aortic valve or the right atrial blood pool (which are all areas of non-specific uptake) and were not included as quantitatively positive even if >1.5X LVBP SUV.

Diagnostic reclassification indices

The concordance and discordance of cardiac FDG PET clinically reported interpretations and the quantitative re-analysis were evaluated for all exams. In order to assess the overall impact of quantitative re-analysis, net diagnostic reclassification indices (NDI) were calculated as:

$$NDI = \frac{\text{Negative studies reclassified as positive} - (\text{Positive studies reclassified as negative})}{(\text{Total number of studies})}$$

Using this approach, a positive NDI would indicate a net upward reclassification by quantita-

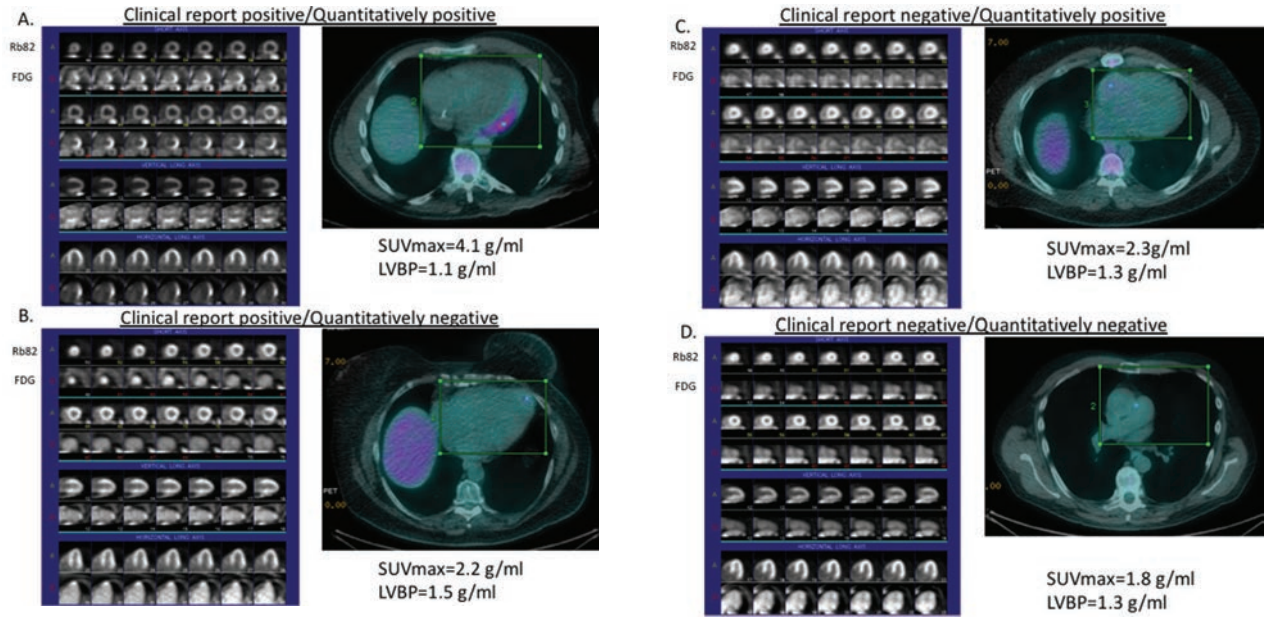

Fig. 1. (A-D) Examples of normalized images used for initial clinical visual report interpretation and FDG-PET fused images displayed in a 0-7g/ml SUV scale. Blue dot in fused image identifies voxel containing SUVmax. A) Concordantly positive images using both visual and quantitative interpretations, B) Clinical report positive/quantitatively re-classified negative example, C) Clinical report negative/quantitatively re-classified positive example, SUVmax in RA free wall, D) Clinical report negative/quantitatively re-classified positive example; note that SUVmax is in the left coronary cusp and therefore the displayed slice does not show myocardium. (LVBP: left ventricular blood pool SUV, used for reference and quantitative threshold)

tive re-analysis, from clinically reported negative to positive quantitative re-analysis, and a negative NDI would indicate a net downward reclassification, from clinically reported positive to negative quantitative re-analysis. It should be noted is that the smaller the total number of exams, the larger the NDI may appear, so with disparate cohort sizes a "negative" or "positive" NDI is of more utility than the value of the NDI itself.

Intervention Analysis

A 'gold standard' for CS diagnosis is difficult to define, as the traditional gold standard of endomyocardial biopsy has poor sensitivity and relies sampling a region of active inflammation. In this context, we analyzed clinical interventions occurring after FDG PET exams and their relationship to reclassification of FDG positivity to see if a quantitative interpretation had a relationship to downstream events. In particular, we focused on downstream interventions that were likely related to the visual interpretation from the initial clinical report, as this was the only interpretation available to clinicians (quantitative analysis was done retrospectively). These downstream interventions included those associated with referring physician practice/bias (immunosuppression initiation/titration and/or ICD placement outside of traditional ICD guidelines (e.g. LVEF<35%, secondary prevention)). New ICD placement after the study (including whether or not the decision for ICD placement was solely on the basis of the PET findings) and immunosuppression initiation or dose increase after the study were also included. Medication initiation after the study was included if it was prescribed in the first follow up appointment after the study with a sarcoidosis specialist.

Events Analysis

Electronic medical records were retrospectively reviewed for clinical events including admissions for CHF, arrhythmia, and death. Arrhythmias included atrial fibrillation/ablation for atrial fibrillation, VT/admissions for VT ablation, AV block, ICD firing and PVC ablation. All patients with online St. Jude's or Medtronic devices (29 patients) were evaluated for ICD data. Patients who were admitted for ICD discharges had appropriate discharges based on review of the EMR. ICD procedure notes and provider notes were reviewed for the reason for ICD placement. Events analysis data included those that extended from the time of the exam to the time of a subsequent exam or February 2017, whichever came first. As some patients had multiple exams, events were examined in two ways. First, all exams were studied and events included those that occurred prior to the next exam. Second, only the initial exams were studied and events included only those that occurred prior to the second exam.

Statistical analysis

Analyses were performed with GraphPad Prism (version 7.01, GraphPad Software, USA). Unpaired T test was used to compare means. Tukey's multiple comparisons test was used when necessary.

Results

Clinical characteristics of study groups

A total of 162 exams during the study timeframe were evaluated (Figure 2). Eight exams from seven patients, had diffuse/non-specific uptake and were not included in the analysis, leaving 154 interpretable exams from 125 patients (20 patients had 2 exams, 5 had 3 exams). Sixty patients met CS criteria, 25 without extra-cardiac sarcoidosis ("isolated CS"). Sixty-five patients did not meet CS criteria. Demographic data is shown in Table 1.

Reclassification

We re-analyzed all 154 exams using quantitative techniques and compared these results to the visual interpretation from the clinical report. Twenty-two exams were originally deemed FDG positive on the clinical report but were judged to be negative by quantitative re-analysis (SUVmax <1.5x LVBP), yielding a NDI of -13.0%. This negative NDI occurred in exams from patients meeting any criteria for CS (-16.7%) JMHW/HRS CS (-8.6%), isolated CS (-28%), and no CS (-9.2%). These reclassification indices for FDG positivity indicate that there was an overall downward classification from positive to negative using quantitative re-analysis, see Table 2.

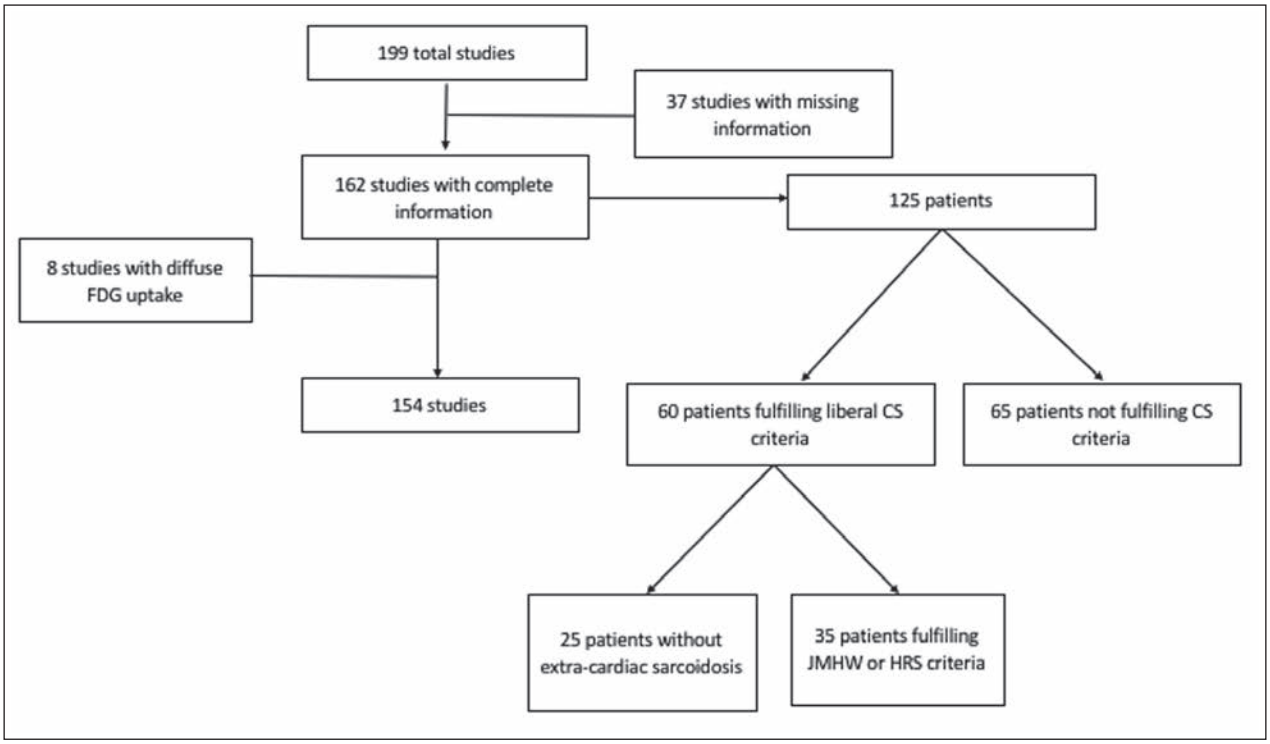

Fig. 2. Study schema

Quantitative FDG measurements

In exams that were clinically reported as visually FDG positive, quantitative re-analysis gave an SUVmax that was greater than in those that were clinically reported as visually negative (4.6±0.3 vs. 2.1±0.1 g/ml, p<0.0001, Table 3). This is consistent with prior studies showing SUVmax is a good marker of visual positivity in FDG PET for CS (4,7).

In exams classified as concordantly positive on both the clinical report and quantitative re-analysis, SUVmax was greater than those classified as concordantly negative. This occurred when all exams were studied (5.5±2.3 vs. 2.1±0.5 g/ml (p<0.0001)) as well as when those from patients meeting any CS criteria (5.8±2.7 vs. 2.2±0.5 g/ml, p<0.0001), JHMW/HRS CS (6.5±2.2 vs. 2.3±0.5 g/ml, p<0.0001) and non-CS (4.8±1.3 vs. 2.0±0.5 g/ml) cohorts were examined, see Figures 3 and 4. For isolated CS patients the difference (4.7±3.2 vs. 2.2±0.5 g/ml) did not reach statistical significance (p=0.07, n =25).

SUVmax was similar in exams where the clinical report was positive but the quantitative re-analysis was negative (2.5±0.8 g/ml; n=22) compared to exams that were negative on both the clinical report and quantitative re-analysis (2.1±0.5; n=80), see Table 3 and Figure 3. These findings were similar in the total CS cohort (2.7±1.0 vs. 2.2±0.5 g/ml, p=0.94), JMHW/HRS CS cohort (2.4±1.0 vs. 2.3±0.5 g/ml, p=0.99) and non-CS cohort (2.2±0.3 vs. 2.0±0.5, p=0.88), see Figure 4. These findings show that some exams that were clinically reported as positive using visual interpretation had low intensity SUVmax and raises the question of normalization during visual on the nuclear cardiology display.

Intervention Analysis

141 out of 154 patients had follow up visits noted in the chart. For interventions potentially related to the FDG PET exam, we looked at interventions that occurred prior to the next exam (if applicable). There was a mean follow up duration of 33.8 days±44.5 from the time of the imaging study to the time until the follow up visit or telephone encounter referencing the study.

The most common intervention (n=46) after an exam was the increase or initiation of prednisone

Table 1. Baseline characteristics of patient cohorts

		All patients (n=125)	Cardiac Sarcoidosis –total (n=60)	Cardiac Sarcoidosis - JMHW or HRS (n=35)	Isolated CS (n=25)	No CS (n=65)
Age		56.3 (12.5)	55.7 (12.2)	55.3 (12.8)	56.4 (11.6)	57.0(12.7)
Gender	Female	42 (34%)	19 (32%)	11 (31%)	8 (32%)	23 (35%)
	Male	83 (66%)	41 (68%)	24 (69%)	17 (68%)	42 (65%)
Ethnicity	Caucasian	67 (54%)	29 (48%)	16 (46%)	13 (52%)	38 (58%)
	African American	38 (30%)	22 (37%)	14 (40%)	8 (32%)	16 (25%)
	Hispanic	10 (8%)	5 (8%)	3 (9%)	2 (8%)	5 (8%)
	Other	7 (6%)	3 (5%)	1 (3%)	2 (8%)	4 (6%)
	Asian	3 (2%)	1 (2%)	1 (3%)	0	2 (3%)
Extra Cardiac Sarcoidosis	Biopsy proven	26 (20%)	17 (28%)	17 (49%)	0	9 (14%)
	Clinical diagnosis	25 (20%)	17 (28%)	17 (49%)	0	8 (12%)
ECG	RBBB	14 (11%)	9 (15%)	9 (26%)	0	5 (8%)
	LBBB	6 (5%)	3 (5%)	1 (3%)	2 (8%)	3 (5%)
	AV Block or Paced	27 (22%)	19 (32%)	10 (29%)	9 (36%)	8 (12%)
	PVC	8 (6%)	2 (3%)	1 (3%)	1 (4%)	6 (9%)
EF (gated Rb82)		39 (16.4)	33.2 (17.9)	40.2 (18.7)	23.6 (13.4)	45.0 (22.6)
Endomyocardial Biopsy	Performed	14 (11%)	7 (12%)	3 (9%)	4 (16%)	7 (11%)
	Positive	2 (2%)	2 (3%)	2 (6%)	0	0
JMHW	Positive	13 (10%)	13 (22%)	13 (37%)		
	Positive but no extra-cardiac sarcoidosis	25 (20%)	25 (42%)		25 (100%)	
HRS	Positive	34 (27%)	34 (57%)	34 (97%)		
Patients with CS by both HRS and JMHW criteria		12 (10%)	12 (20%)	12 (34%)		
Patients with CS by either HRS or JMHW criteria		35 (28%)	35 (58%)	35 (100%)		
Data presented as percentages or mean (SD) as appropriate.						

and/or adjunctive immunosuppression, see Table 4. For the all exams cohort, the most interventions were performed in the quantitative re-analysis and clinical report positive group. Five (10%) ICDs were placed (of which 2 were not indicated by other standard ICD criteria (e.g LVEF)). In the quantitative re-analysis negative and clinical report positive group, 4 (18%) ICDs were placed after the initial study. Two

Table 2. Net Diagnostic Reclassification Indices

All exams (n=154)			
	Initial Clinical Report		
Quantitative Re-Analysis	Positive	Negative	Totals
Positive	50	2	52
Negative	22	80	102
Totals	72	82	154
NDI = (2/154) - (22/154) = -13.0%			
Per patient by first exam			
Cardiac Sarcoidosis- total (n=60)			
	Initial Clinical Report		
Quantitative Re-Analysis	Positive	Negative	Totals
Positive	28	1	29
Negative	11	20	31
Totals	39	21	60
NDI = (1/60) - (11/60) = -16.7%			
Cardiac Sarcoidosis (JMHW/HRS) (n=35)			
	Initial Clinical Report		
Quantitative Re-Analysis	Positive	Negative	Totals
Positive	18	1	19
Negative	4	12	16
Totals	22	13	35
NDI= (1/35) – (4/35) = -8.6%			
Isolated CS (n=25)			
	Initial Clinical Report		
Quantitative Re-Analysis	Positive	Negative	Totals
Positive	10	0	10
Negative	7	8	15
Totals	17	8	25
NDI = (0/25) – (7/25) = -28.0%			
No Cardiac Sarcoidosis (n=65)			
	Initial Clinical Report		
Quantitative Re-Analysis	Positive	Negative	
Positive	13	0	13
Negative	6	46	52
Totals	19	46	65
NDI = (0/65) - (6/65) = -9.2%			

of 4 ICDs had CS listed as a reason for their implantation, with an average placement 59 days post study. Prednisone or another immunosuppressant was initiated or dose increased in 11 (50%) patients in this group after the initial study. Similar patterns can be seen when dividing the all exams cohort into the CS total, CS and the isolated CS groups. The no CS group, defined by not meeting JMHW/HRS/JMHW without extra-cardiac sarcoidosis, had a total of 4 ICDs placed. Interestingly, this group had one patient for whom a ICD was placed and CS was listed as a reason for placement. Six patients (4 in the quantitative and clinical report positive and 2 in quantitative negative and clinical report positive group) had immunosuppression initiated or increased.

Table 3. Averages of SUVmax

All exams (n=154)		
	Initial Clinical Report	
Quantitative Re-Analysis	Positive	Negative
Positive	5.5 (2.3)[ab]	2.85 (0.8)
Negative	2.5(0.8)[b]	2.1 (0.5)[a]
Per patient by first exam		
Cardiac Sarcoidosis- total (n=60)		
	Initial Clinical Report	
Quantitative Re-Analysis	Positive	Negative
Positive	5.8 (2.7)[cd]	3.4 (0)
Negative	2.7(1.0)[d]	2.2 (0.5)[c]
Cardiac Sarcoidosis (JMHW/HRS) (n=35)		
	Initial Clinical Report	
Quantitative Re-Analysis	Positive	Negative
Positive	6.5 (2.2)[ef]	3.4 (0)
Negative	2.4 (1.0)[f]	2.3 (0.5)[e]
Isolated CS (n=25)		
	Initial Clinical Report	
Quantitative Re-Analysis	Positive	Negative
Positive	4.7 (3.2)	
Negative	2.8 (1.0)	2.2 (0.5)
No CS (n=65)		
	Initial Clinical Report	
Quantitative Re-Analysis	Positive	Negative
Positive	4.8 (1.3)[gh]	
Negative	2.2(0.3)[h]	2.0 (0.5)[g]
[a-h] Significant difference (p<0.01) between values with the same letter. Values presented as Mean (SD)		

Events Analysis

For clinical events, we analyzed the first event following a study in order to judge the effect of that study's findings on clinical events. A total of 32 events occurred following 154 exams with a mean duration of 240±209 days from exam until event, see Table 5. In the all exams group, the cohort with the highest percentage of events had exams that were reported as negative on both the clinical report and quantitative re-analysis, where 17 events occurred (in 66 patients). Five (10%) exams were followed by admissions for arrhythmias and/or CHF. The majority of arrhythmias were for afib/ablation and PVC ablation (8 of 12). There were no deaths in this group. The average time until admission was 231 days. Alternatively, in the quantitatively negative/clinical report positive group, 4 events occurred (17 patients), with 2 (10%) admissions post-exam and 2 (9%) deaths in this group. One of these was an admission after VT that led to an ICD shock 15 days post exam (on a background of an ejection fraction of 26%). The

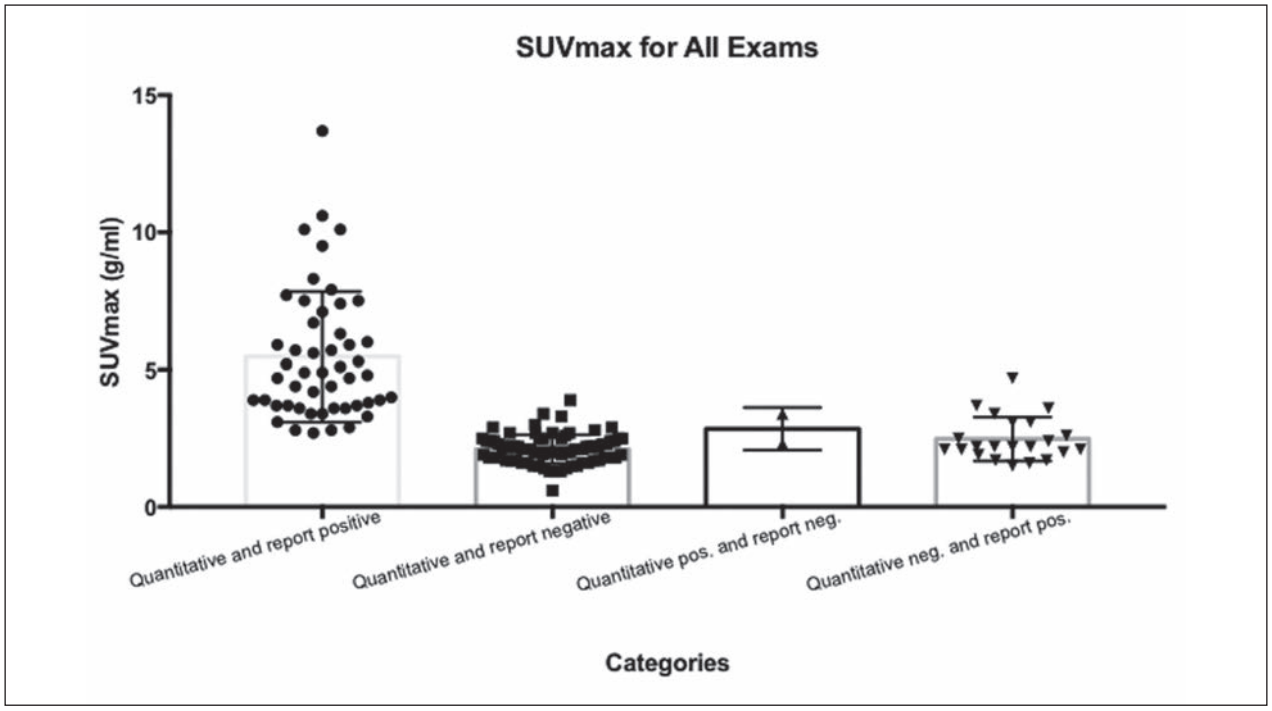

Fig. 3. Average SUVmax for All Exams with Mean and SD. Scatterplot demonstrating the distribution of SUVmax

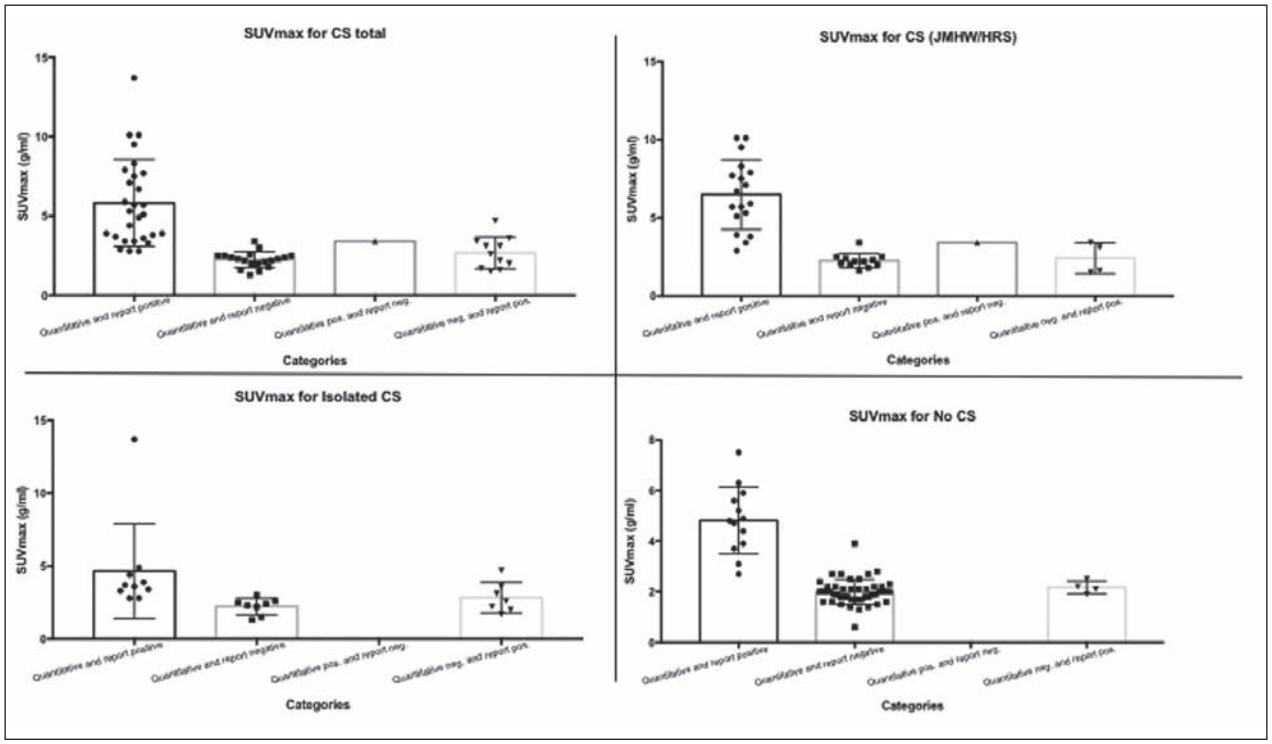

Figure 4. Average SUVmax for Cardiac Sarcoidosis total, Cardiac sarcoidosis – (JMHW/HRS), Isolated CS and No CS groups with Mean and SD. Scatterplots demonstrating the distribution of SUVmax.Average SUVmax for All Exams with Mean and SD. Scatterplot demonstrating the distribution of SUVmax

Table 4. Intervention analysis

	Patients	Exams	Interventions	Prior ICD	ICD placed	ICD placed			Prednisone initiated or dose increased	Other Immunosupp. initiated
						Either VT or low EF	CS listed as reason	Average Number of Days post study		
All exams (n=154)										
Quantitative and report positive	41	50	36	35 (70%)	5 (10%)	3	2	244	20 (40%)	11 (22%)
Quantitative and report negative	66	80	9	38 (48%)	5 (6%)	3	3	113	1 (1%)	3 (4%)
Quantitative pos. and report neg.	1	2	1	0	1 (50%)	1	1	522	0	0
Quantitative neg. and report pos.	17	22	15	13 (59%)	4 (18%)	2	2	59	6 (27%)	5 (23%)
Per patient by first exam										
Cardiac sarcoidosis-total (n=60)										
Quantitative and report positive	28	28	25	20 (71%)	4 (14%)	2	2	42	15 (54%)	6 (21%)
Quantitative and report negative	20	20	4	13 (65%)	2 (10%)	1	2	164	1 (5%)	1 (5%)
Quantitative pos. and report neg.	1	1	1	0	1 (100%)	1	1	522	0	0
Quantitative neg. and report pos.	11	11	7	5 (45%)	3 (27%)	2	1	74	3 (27%)	1 (9%)
Cardiac Sarcoidosis- (JMHW/HRS) (n=35)										
Quantitative and report positive	18	18	21	12 (67%)	3 (17%)	1	2	42	12 (67%)	6 (33%)
Quantitative and report negative	12	12	4	7 (58%)	2 (17%)	1	2	164	1 (8%)	1 (8%)
Quantitative pos. and report neg.	1	1	1	0	1 (100%)	1	1	522	0	0
Quantitative neg. and report pos.	4	4	3	2 (50%)	1 (25%)	1	0	7	1 (25%)	1 (25%)
Isolated CS (n=25)										
Quantitative and report positive	10	10	4	8 (32%)	1 (10%)	1	0	0	3 (30%)	0
Quantitative and report negative	8	8	0	6 (24%)	0	0	0	0	0	0
Quantitative pos. and report neg.	0	0								
Quantitative neg. and report pos.	7	7	4	3 (12%)	2 (29%)	1	1	108	2 (29%)	0
No Cardiac Sarcoidosis (n=65)										
Quantitative and report positive	13	13	5	6 (46%)	1 (8%)	1	0	589	4 (31%)	0
Quantitative and report negative	46	46	2	16 (35%)	2 (4%)	1	0	26	0	0
Quantitative pos. and report neg.	0	0								
Quantitative neg. and report pos.	6	6	3	4 (67%)	1 (17%)	0	1	14	1 (17%)	1 (17%)

patient ultimately died after being found to be bacteremic 98 days post exam. The other fatal event occurred 713 days post exam in a patient awaiting heart transplantation.

Discussion

The aim of this study was to compare the potential diagnostic reclassification of FDG PET for cardiac sarcoidosis using quantitative versus visual analysis. Our study had a number of significant findings. First, there was a net downward diagnostic reclassification observed, from positive to negative, for all patient cohorts when quantitative re-analysis was compared to the clinical report that used visual interpretation. Second, following 11 out of 22 exams reclassified as from positive to negative by quantitative re-analysis, patients had immunosuppression initiated and/or increased and 4 had ICDs placed. If clinicians had seen a negative interpretation of the imaging, it is possible that these interventions would not have been performed. Lastly, event rates were low in patients referred for FDG PET who do not meet clinical criteria for CS.

Regarding diagnostic reclassification, the overall 13% negative NDI reflected 22/154 exams that were reclassified from positive on the initial clinical

Table 5. Events analysis

				Admission			Arrhythmias					
	Patients	Exams	Events	CHF	Arrhythmia	Both	Afib/ Ablation	AV block	PVC ablation	VT/VT ablation	ICD firing	Death
All exams (n=154)												
Quantitative and report positive	41	50	10	1 (2%)	1 (2%)	3 (6%)	2	0	0	2	0	5 (10%)
Quantitative and report negative	66	80	17	5 (6%)	12 (15%)	0	4	1	4	1	2	0
Quantitative pos. and report neg.	1	2	1	0	0	1 (50%)	1	0	0	0	0	0
Quantitative neg. and report pos.	17	22	4	1 (5%)	1 (5%)	0	1	0	0	0	0	2 (9%)
Per patient by first exam												
Cardiac sarcoidosis-total (n=60)												
Quantitative and report positive	28	28	8	2 (7%)	1 (4%)	2 (7%)	1	0	0	2	0	3 (11%)
Quantitative and report negative	20	20	7	4 (20%)	3 (15%)	0	0	0	1	1	1	0
Quantitative pos. and report neg.	1	1	1	0	0	1 (100%)	1	0	0	0	0	0
Quantitative neg. and report pos.	11	11	3	1 (9%)	0	0	0	0	0	0	0	2 (18%)
Cardiac Sarcoidosis- (JMHW/HRS) (n=35)												
Quantitative and report positive	18	18	4	1 (6%)	1 (6%)	1 (6%)	1	0	0	1	0	1 (6%)
Quantitative and report negative	12	12	4	2 (17%)	2 (17%)	0	0	0	0	1	1	0
Quantitative pos. and report neg.	1	1	1	0	0	1 (100%)	1	0	0	0	0	0
Quantitative neg. and report pos.	4	4	1	0	0	0	0	0	0	0	0	1 (25%)
Isolated CS (n=25)												
Quantitative and report positive	10	10	4	1 (10%)	0	1 (10%)	0	0	0	1	0	2 (20%)
Quantitative and report negative	8	8	3	2 (25%)	1 (13%)	0	0	0	1	0	0	0
Quantitative pos. and report neg.	0	0	0	0	0	0	0	0	0	0	0	0
Quantitative neg. and report pos.	7	7	2	1 (14%)	0	0	0	0	0	0	0	1 (14%)
No Cardiac Sarcoidosis (n=65)												
Quantitative and report positive	13	13	2	0	0	1 (8%)	1	0	0	0	0	1 (8%)
Quantitative and report negative	46	46	7	1 (8%)	6 (13%)	0	3	1	1	1	0	0
Quantitative pos. and report neg.	0	0	0	0	0	0	0	0	0	0	0	0
Quantitative neg. and report pos.	6	6	0	0	0	0	0	0	0	0	0	0

report to negative by quantitative re-analysis. These exams had an average SUVmax of 2.5 g/ml, which was similar to the average SUVmax of the concordant negative group (2.1 g/ml). If quantitative analysis had been used initially, these patients would not have been classified as having inflammation on their exams. We posit that the overall downward reclassification was due to the enhanced specificity of quantitative re-interpretation compared to the traditional nuclear cardiology reading software used to interpret these exams for their initial clinical read. All nuclear cardiology reading programs currently available (WLCQ, Invia4DM, Cedars-Sinai, Emory, Myovation, Syngo, etc.) normalize the intensity of images to the pixel with the highest counts in the study. This is an intentional design attribute of these systems so that there is visual similarity in display intensity of studies that can have up to a four-fold difference in counts per pixels (e.g. low dose/high dose rest/stress myocardial perfusion imaging studies). In fact, none of these programs to our knowledge offers an SUV-scaled display where images are displayed relative to their absolute intensity. However, in 'hot spot' imaging techniques like FDG PET imaging, the intensity of the FDG uptake and target-to-background ratio is intrinsically important to the interpretation. Therefore, the use of normalized display systems for FDG PET imaging may not be valid. Recent ASNC/SNMMI guidelines for FDG PET for cardiac sarcoidosis suggest that the use of quantitative

display systems and interpretive strategies may be useful (1), realizing there is not clarity about the optimal method for quantification.

Our quantitative strategy relied upon the use of a cardiac SUVmax threshold of 1.5-times left ventricular blood pool. We have previously reported on the derivation of this threshold for cardiac sarcoidosis, its reproducibility, relationship to adverse events, and utility in defining imaging response to immunosuppression (4,7). We have also reported on the use of the volume and volume-intensity of FDG-positive myocardium for diagnostic and treatment response purposes. We chose SUVmax as our quantitative variable for this study due to its ease of use and validity. The other methods to quantify abnormal cardiac FDG uptake in CS PET studies (5,6,8) would find similar enhanced specificity of interpretation compared to visual analysis and our results were not fundamentally different when using volumetric measures (data not shown).

One of the most striking potential impacts of this study was the data showing that studies where there was low-intensity FDG uptake that was clinically reported as positive, but were negative on quantitative re-analysis, were followed by a number of downstream medical interventions but few clinical events. Following 22 negatively reclassified exams, 15 patients either had ICDs implanted and/or immunosuppression started/increased. Due to the retrospective nature of our study and limitations of EMR documentation, there is no definitive way to ensure that the reported clinical read of the studies using visual analysis led to these interventions. However, these interventions are commonly related in practice to the results of FDG PET imaging. Therefore, it is not unreasonable to assume that a large number of these interventions, particularly the 11 patients who had immunosuppression started/increased, were likely significantly related to the initial clinical reports. It is concerning that one of these patients who had immunosuppression increased died from sepsis/bacteremia. Therefore, shifting from a solely visual analysis to quantitative analysis could in theory reduce the number of patients who are either given the diagnosis of active cardiac inflammation and treated with potentially toxic immunosuppression or who get exposed to the potential complications of ICD implantation.

Clearly, one concern of the net downward diagnostic reclassification of quantitative interpretation of FDG PET for CS is a reduced sensitivity for disease detection. We examined clinical events that occurred downstream of the studies. Both visually and quantitatively positive studies had the highest SUVmax (5.5 g/ml), consistent with prior studies that the intensity of FDG uptake is an important predictor of events in CS (4). There were only 4 clinical events following the 22 exams that were down-classified. As discussed above, one death occurred from bacteremia and one event >2 years after the exam. Therefore, our interpretation of the data suggests that the downward reclassification was not associated with a high event rate. Clearly, a confounder to this conclusion stems from the fact that 11/17 patients were treated with immunosuppression (likely) due to the clinical read. However, 31/41 (76%) of patients in the concordantly clinical report positive and quantitative re-analysis positive group were also treated with immunosuppression and, nonetheless, had a higher event rate. Therefore, this suggests that the down-classified studies were not from patients who had an overall high risk.

Lastly, we evaluated the clinical impact of interpretive reclassification in patients who did not meet any clinical criteria for CS. These patients represent a significant portion of patients referred for FDG PET imaging, due to unexplained cardiomyopathies and/or arrhythmias. Interestingly, there was a low clinical event rate in non-CS patients. This may be explained by several factors, including a higher average ejection fraction in this cohort (45±23% vs. 33±18% in the CS cohort). Secondly, these patients obviously did not have higher risk features that would allow them to meet the JMHW/HRS criteria. This is very preliminary data, but it suggests that the use of FDG PET imaging in these patients does little to define downstream risk of events. It is possible that non-CS patients who were concordantly FDG positive by both visual and quantitative measures represent a spectrum of an otherwise undiagnosed "inflammatory cardiomyopathy". This particular patient group and the use of FDG PET imaging in patients with no high-risk features for CS warrant further future study.

Our study has limitations that we acknowledge. First, it is a single-center, retrospective experience of highly selected patients where there is clearly a referral bias and institutionally-defined practice patterns. Nonetheless, as a quaternary referral center for advanced sarcoidosis, our practice pattern gen-

erally reflects current advanced practice in the care of cardiac sarcoidosis. Another potential limitation is the single-center nature of the nuclear lab interpretation of the initial clinical read. However, our nuclear cardiology lab and readers include experienced academic nuclear cardiologists, suggesting that if our readers were interpreting studies using this visual approach that many other institutions are using similar methods. A major limitation of our study was that the overall low event rates, which may be due to the study being underpowered, which did not allow for generation of a survival curves or statistical comparisons across multiple cohorts. Clearly, a larger, multi-center strategy to evaluate interpretive methodologies in FDG PET for CS is needed. Until this framework is further developed, and the optimal method of quantitative analysis is defined, analysis using a quantitative analysis to corroborate visual findings may be the best approach to FDG PET for CS interpretation.

Overall, study demonstrates the limited utility of traditional visual analysis and argues for further use of standardized methods of quantitative analysis for FDG PET for CS and potentially improve the optimal use of interventions in CS patients.

Relationship with industry: Dr. Miller receives grant funding from Bracco, Inc. for FDG PET examinations in cardiac sarcoidosis unrelated to the present study

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