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Deep learning approaches to predict late gadolinium enhancement and clinical outcomes in suspected cardiac sarcoidosis.

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To the Editor,

Cardiac sarcoidosis is an underdiagnosed cardiac condition at high risk for clinical events (1). Despite current guidelines, there is an unmet clinical need for stratifying the prognosis of these patients. A threshold of 5.7% of late gadolinium enhancement (LGE) has been reported as being highly prognostically relevant (2). Further, recent progress in artificial intelligence has enabled automated detection and prognosis stratification in many diseases (3). The aim of the present study was to establish a proof-of-concept that a deep learning model could predict late gadolinium enhancement burden and clinical outcomes in patients with suspected cardiac sarcoidosis using native LGE cardiac magnetic resonance (CMR) imaging frames. With Institutional Review Board approval (GCO-01-1032) and written informed consent, patients with clinical suspicion of active CS due to established extra-cardiac involvement and/or clinical presentation consistent with active cardiac sarcoidosis were prospectively recruited and followed-up at Mount Sinai Hospital, New York. Each patient underwent simultaneous cardiac magnetic resonance (MR) with late gadolinium enhancement (LGE) sequences on a hybrid MR/PET system (Biograph-mMR, Siemens Healthineers) as previously described (4). The input was an LGE-sequence CMR image of the base of the heart (Figure 1, A). One frame corresponded to one patient (i.e one sample). Two model architectures were studied: InceptionV3 (5) and ResNet50 (6). Three different models were compared for each of these two architectures: random weights initiation, pre-training on ImageNet, or pre-training on RadImageNet (7). A flatten layer and a dense layer of 512 units with a 50% of dropout were added on top of the base models. Models were trained for two binary classification tasks: (i) predicting the presence of a LGE lesion (above 5.7% of the myocardium, defining $LGE_{5.7+}$ group), (ii) predicting the occurrence of a clinical event (defined as the occurrence of either ventricular tachycardia (VT), complete heart block (CHB)/acute heart failure (AHF) requiring hospitalization/death during follow-up). Hyperparameters were set as follows: Learning rate: 0.001, number of epochs: 100 for all models for comparison, batch size: 8, stratified K-fold with K = 4, all models' layers were trainable. Models' explainability was studied with Keras' class activation maps method Grad-Cam. A total of 116 patients were included. Median age was 56 years [50-62], 45 patients (40%) were women. Median left ventricular ejection fraction was 59% [51-65]. Heart rhythm society criteria for probable cardiac sarcoidosis were met in

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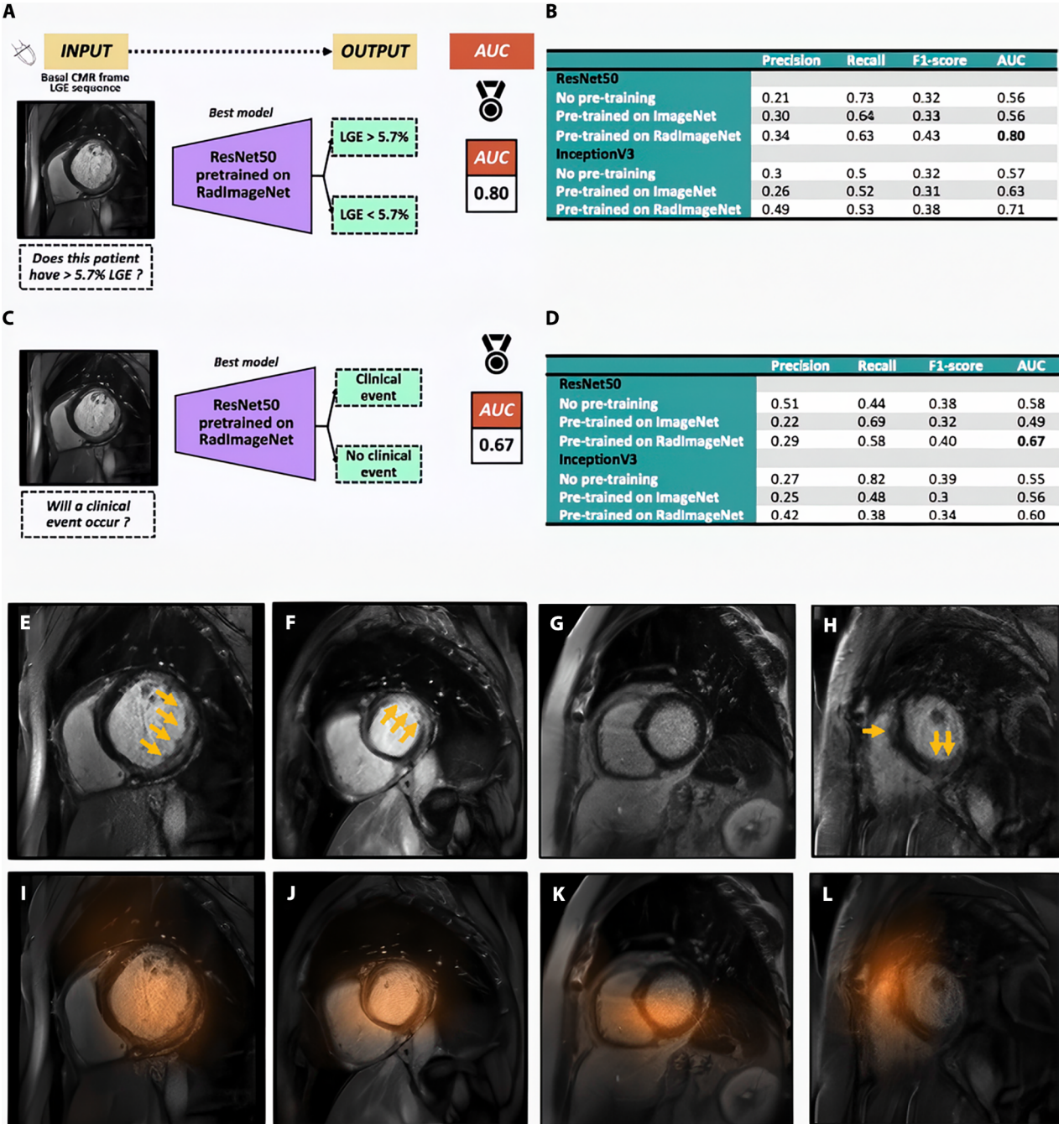
52 patients (45%). Extra cardiac sarcoidosis was biopsy-proven in 91 patients (78%). Median follow-up was 5.4 years [4.8-5.9]. Overall, 19 (16%) had significant LGE lesions (>5.7%). A total of 66 patients (57%) had no LGE lesions. Mean LGE burden was 3.2% (± 8) for the whole series and 12% (±12) in the $LGE_{5.7+}$ group. Median CMR-to-event time was 1.9 years [0.1-3.1]. A total of 23 (20%) developed a clinical event (9 VT, 3 CHB, 7 AHF, 4 deaths). Model performances are reported in Figure 1. For both tasks, the highest AUCs were obtained with a ResNet50 architecture, pretrained on RadImageNet (Figure 1, A). Best AUC for LGE lesion prediction was 0.80 (positive predictive value: 34%, negative predictive value: 88%; Figure 1, A and C). Best AUC for clinical event prediction was 0.67 (Figure 1, B and D). Class activation maps demonstrated relevant patterns of activation, establishing a proof-of-concept that LGE can be predicted using native CMR imaging (Figure 1, E-L). This study has several limitations. First, we acknowledge that only basal CMR frames were used rather than full imaging sequences. The latter strategy should be explored. However, its implementation is not straightforward and would consist in including the use of multiple models with a combined prediction strategy or in using a full CMR sequence framed as a video input feature. Second, this study is limited by the lack of prior determination of CS in the study cohort; we enrolled patients with a clinical suspicion of CS based on the history of sarcoidosis and cardiac symptoms and/or arrhythmias suggestive of sarcoidosis, which therefore reflects a real-world population of patients undergoing PET and MR imaging. Third, only HRS diagnostic criteria were used although other criteria have been published. Fourth, the present findings could be applicable to any cardiomyopathy, not unique to cardiac sarcoidosis per se. However, we restricted our approach to cardiac sarcoidosis due to the clinical risk prediction unmet challenge and the high prevalence of adverse outcomes. Our model did not aim at predicting true cardiac sarcoidosis but rather at predicting LGE burden in a classical clinical setting, irrespective of definite or endomyocardial biopsy proven sarcoidosis. Fifth, there are well established, easily performed myocardial LGE quantification methods available, to determine myocardial scar burden, and this has been applied to ischemic and non-ischemic cardiomyopathies. However, previous attempts to detect LGE from native CMR frames required large amounts of data and have relied on segmenting the left ventricle, used images with pre-contoured LGE lesions or tried a two-step pipeline with a PCA followed by a kernel method algorithm (8). Our pipeline allows the use of native CMR frames and demonstrated good performance using a small sample size. Our aim was not to provide a readily usable solution but rather evaluate, as a preliminary effort, the ability of a deep learning framework to extract and "understand" the notion of LGE and using it for clinical outcome prediction. In this context, we show that although LGE may be effectively detected, performances for clinical outcomes prediction were poor. Further work should include a framework that utilizes multiple slices and/or multimodality input features, either from imaging modalities such as ^{18}F-fluorodeoxyglucose PET data, or clinical tests, to improve clinical predictions. Lastly, with regards to pretraining, we compared state-of-the art model architectures with the latest and largest imaging datasets, with the general-purpose ImageNet dataset and the newly developed and publicly available RadImageNet. While no CMR images were present in the RadImageNet dataset (7), pretraining improved model performances. Our results further support the benefits of transfer learning in medical imaging, paving the way to new successful applications especially in rare diseases. To conclude, this study provides proof-of-principle that LGE burden prediction using CMR imaging of patients with cardiac sarcoidosis can be automated through deep learning models. Transfer learning strategies leveraging the RadImageNet dataset significantly and consistently improved models' performances. Expanded models may be explored that combine additional information from multiple image modalities while retaining the robustness and simplicity of an automated Deep Learning framework.



	Precision	Recall	F1-score	AUC
ResNet50				
No pre-training	0.21	0.73	0.32	0.56
Pre-trained on ImageNet	0.30	0.64	0.33	0.56
Pre-trained on RadImageNet	0.34	0.63	0.43	**0.80**
InceptionV3				
No pre-training	0.3	0.5	0.32	0.57
Pre-trained on ImageNet	0.26	0.52	0.31	0.63
Pre-trained on RadImageNet	0.49	0.53	0.38	0.71

	Precision	Recall	F1-score	AUC
ResNet50				
No pre-training	0.51	0.44	0.38	0.58
Pre-trained on ImageNet	0.22	0.69	0.32	0.49
Pre-trained on RadImageNet	0.29	0.58	0.40	**0.67**
InceptionV3				
No pre-training	0.27	0.82	0.39	0.55
Pre-trained on ImageNet	0.25	0.48	0.3	0.56
Pre-trained on RadImageNet	0.42	0.38	0.34	0.60

Figure 1. Late Gadolinium Enhancement Detection in Cardiac Sarcoidosis Using Deep Learning and Transfer Learning strategies. A. Best model pipeline for LGE prediction. B. Best model pipeline for clinical event occurrence prediction. C. Performances according to model architecture and pre-training for LGE prediction. D. Performances according to model architecture and pre-training for clinical event occurrence prediction. E-L. Class activation maps results on the test set with a ResNet50 pretrained on RadImageNet for LGE (> 5.7%) prediction. The determining area of the image is the heart for model classification (positive and negative classes). E.I. True positive. Patient with significant LGE (yellow arrow), with model classifying correctly. F.J. False negative. Patient with significant LGE (yellow arrow). G.K. True negative. Patient with no LGE. H.L. False positive. Patient with non-significant LGE (yellow arrow) classified as LGE+ patient by the model.

Abbreviations: AUC, area under the curve; LGE, late gadolinium enhancement

Author Contributions: L-D.A, X.M and Z.A.F designed the study. L-D.A, P.M.R, S.L, M.G.T collected the data. L-D.A and X.M conducted the statistical analysis. L-D.A, X.M, V.F, P.M.R, S.L, A.D, M.G.T, and Z.A.F analyzed and interpreted the data. L-D.A and X.M wrote the manuscript. All the authors critically reviewed and approved the final version of the manuscript.

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