#### <u>Artificial intelligence and cardiovascular magnetic resonance imaging in myocardial</u> <u>infarction patients</u>

Jun Hua Chong<sup>1,2\*</sup>, Musa Abdulkareem<sup>3,4,5</sup>, Steffen E. Petersen<sup>3,4,5,6†</sup>, Mohammed Y. Khanji<sup>3,4,7†</sup>

\*corresponding author

 $^{\dagger}joint$  last authors

<sup>1</sup>National Heart Centre Singapore, Singapore

<sup>2</sup>Cardiovascular Sciences Academic Clinical Programme, Duke-National University of Singapore Medical School, Singapore

<sup>3</sup>Barts Heart Centre, Barts Health National Health Service Trust, London, United Kingdom

<sup>4</sup>National Institute for Health Research Barts Biomedical Research Centre, William Harvey Research Institute, Queen Mary University of London, London, United Kingdom

<sup>5</sup>Health Data Research UK, London, United Kingdom

<sup>6</sup>The Alan Turing Institute, London, United Kingdom

<sup>7</sup>Department of Cardiology, Newham University Hospital, Barts Health NHS Trust, Glen Road, London E13 8SL, UK

#### Abstract

Cardiovascular magnetic resonance (CMR) is an important cardiac imaging tool for assessing the prognostic extent of myocardial injury after myocardial infarction (MI). Within the context of clinical trials, CMR is also useful for assessing the efficacy of potential cardioprotective therapies in reducing MI size and preventing adverse left ventricular (LV) remodelling in reperfused MI. However, manual contouring and analysis can be timeconsuming with interobserver and intraobserver variability, which can in turn lead to reduction in accuracy and precision of analysis. There is thus a need to automate CMR scan analysis in MI patients to save time, increase accuracy, increase reproducibility and increase precision. In this regard, automated imaging analysis techniques based on artificial intelligence (AI) that are developed with machine learning (ML), and more specifically deep learning (DL) strategies, can enable efficient, robust, accurate and clinician-friendly tools to be built so as to try and improve both clinician productivity and quality of patient care. In this review, we discuss basic concepts of ML in CMR, important prognostic CMR imaging biomarkers in MI and the utility of current ML applications in their analysis as assessed in research studies. We highlight potential barriers to the mainstream implementation of these automated strategies and discuss related governance and quality control issues. Lastly, we discuss the future role of ML applications in clinical trials and the need for global collaboration in growing this field.

# Utility of cardiovascular magnetic resonance imaging in myocardial infarction and the need for automated analysis strategies

Cardiovascular magnetic resonance (CMR) is an important cardiac imaging tool for assessing the prognostic extent of myocardial injury after myocardial infarction (MI) as endorsed by the European Society of Cardiology 2017 guidelines(1) and the Society for Cardiovascular Magnetic Resonance 2020 position paper.(2) Within the context of clinical trials, CMR is useful for assessing the efficacy of potential cardioprotective therapies in reducing MI size and preventing adverse left ventricular (LV) remodelling in reperfused MI. It is currently the gold standard imaging modality to quantify MI size,(3) and it can delineate subendocardial MI as little as 1 gram in size(4) with a high degree of accuracy.(5) Native T1, T2, T2\* and post-contrast T1-mapping (to derive extracellular volume [ECV] mapping)(6) can also enable deeper insights to be garnered into the pathophysiological processes post MI and their associated prognostic significance.

However, manual contouring and analysis can be time-consuming with interobserver and intraobserver variability, which can in turn lead to reduction in accuracy and precision of analysis. There is thus a need to automate CMR scan analysis in MI patients to save time, increase accuracy, increase reproducibility and increase precision. In this regard, automated imaging analysis techniques based on artificial intelligence (AI) that are developed with machine learning (ML), and more specifically deep learning (DL) strategies, can enable efficient, robust, accurate and clinician-friendly tools to be built so as to try and improve both clinician productivity and quality of patient care.

AI refers to computer algorithm-based techniques that enable machines to perform tasks that resemble human intelligence. ML methods encompass supervised, unsupervised, semi-supervised and reinforcement learning methods, amongst others, to achieve AI. DL is a set of advanced ML techniques that are based on artificial neural networks with hidden layers and can be used to detect and differentiate patterns in data. DL is currently the most popular ML method for medical image analysis.

In this review, we discuss important prognostic CMR imaging biomarkers in MI and the utility of current ML applications in their analysis as assessed in research studies (summarised in Table 1 and schematically depicted in Figure 1). We highlight potential barriers to the mainstream implementation of these automated strategies and discuss related governance and quality control issues. Lastly, we discuss the future role of ML applications in clinical trials and the need for global collaboration in growing this field.

# Prognostic implications of myocardial infarction cardiovascular magnetic resonance imaging biomarkers

The parameters of prognostic importance with clinical implications that may be amenable to automated analysis are volumetric analysis, infarct size, area at risk, presence of microvascular obstruction (MVO) and size of MVO.

Historically, left ventricular (LV) ejection fraction (EF) and LV volumes have been the established predictors of mortality in patients with coronary artery disease (CAD) and severe LV dysfunction.(7) Previous studies have shown that LV function and LV end-systolic volume (ESV) were the strongest predictors of cardiac death after MI.(8)

MI size refers to the size of the infarcted myocardium and is conventionally demarcated on late gadolinium enhancement (LGE) imaging. Morbidity and mortality post-ST elevation myocardial infarction (STEMI) is closely associated with acute MI size.(9) A meta-analysis of 2,632 patients showed that MI size assessed by CMR or SPECT within 1 month post-primary percutaneous coronary intervention from 10 randomised controlled trials was

strongly associated with heart failure hospitalisation and all-cause mortality at 1 year, with a 20% increase in relative hazard ratio for both these clinical outcomes for every 5% increase in MI size.(10) This further adds to the growing body of evidence that acute MI size is prognostic.

MVO results from the inability to reperfuse the coronary microcirculation in a previously ischaemic region despite revascularisation of the culprit epicardial vessel. MVO can be identified as a dark hypointense core within areas of hyperenhancement on early gadolinium enhancement imaging.(9) Intramyocardial haemorrhage (IMH) can occur if coronary microvasculature injury is very severe after MI, with resultant damaged vessel integrity and extravasation of red blood cells.(11) Both MVO and IMH are associated with larger MI size, adverse LV remodelling and overall worse clinical outcomes.(12) In general, prognosis worsens with larger MI size, with patients also more likely to have MVO and IMH with larger MI size. Prognosis for STEMI patients with MVO is worse than those without MVO.(13) Prognosis is worst for patients with MVO and IMH.(11)

The area-at-risk (AAR) refers to the myocardial territory supplied by the infarct-related culprit artery that was at risk of infarction and would have infarcted if revascularisation and reperfusion had not taken place to salvage the viable myocardium. The myocardial salvage index (MSI) normalises MI size reduction to AAR and as such is a more sensitive marker compared with MI size alone to assess cardioprotective therapy efficacy.(14) Post-contrast T1-mapping has recently demonstrated promise as an alternative technique to gadolinium enhancement imaging in quantifying MI size.(15) T1-mapping has the potential to complement clinical and imaging parameters and biomarkers to optimise risk stratification in MI patients.(9) Oedema, assessed by CMR using T2-mapping, occurs both in the viable and non-viable myocardium during the first week of a reperfused STEMI in the clinical setting.(16–19) Oedema-based area-at-risk measured by CMR can be used to assess myocardial salvage in clinical cardioprotection studies but the appropriateness of this has been called into question.(9)

#### Basic concepts of machine learning in cardiovascular magnetic resonance imaging

Important image characteristics or features such as image contrast, noise characteristics, texture and motion are highlighted as part of a designed feature set to create a ML model that is trained using data. The model training, e.g. for image segmentation problems, involves using a ML method that allows the model to learn and optimise the parameters of the mathematical model from a set of CMR studies with ground truth segmentations performed by the human expert. The trained model is then used to predict segmentations. The training algorithm extracts the parts of the data that are important for the prediction task and collates the information together to produce the prediction result. ML models can perform either classification or regression tasks. Classification tasks involve discrete labels such as determination of the presence or absence of disease. Regression tasks involve continuous variables such as quantifying the percentage of infarcted myocardium of patients with an acute MI. The training dataset should be sufficiently large with representative variability to optimise performance. A validation dataset is used to evaluate a model's performance and prevent model overfitting.

It has been challenging to identify optimal discriminative features to create ML systems for a given task. In order to circumvent the need to design these discriminative features, DL methods can be applied that can learn directly (end-to-end learning) from the training dataset. In myocardial contouring for example, DL methods will learn the image features that are most useful for predicting myocardial contour locations. A specific type of DL network known as convolutional neural network (CNN) is often used in image analysis-associated tasks. A typical CNN is made up of multiple layers including convolution layers, pooling layers, fully connected layer, skip layers and softmax layer.(20) Deep CNNs are complex and can contain millions of weights, and although the features resulting from the intermediate layers contain information relevant to the task, it is often difficult to interpret how the predictions are actually made or why the network might have failed to make the accurate prediction.

Depending on the availability of reference labels in the training dataset, ML algorithms can be grouped into supervised versus unsupervised learning. In supervised learning, training data of varying pathological status are labelled by human domain experts. In unsupervised learning, hidden structures within the training data are discovered during training. There are different ML methods suited to the varying complexities of the image analysis task. Some of ML methods often encountered in AI literature include linear regression,(21) support vector machines (SVM),(22) decision trees,(23) boosting methods,(24) linear discriminant analysis(25) and ensemble method.(26) In linear discriminant analysis for instance, ML model parameters are estimated by assuming a simple functional relationship between the data and the labels to separate data into normal and abnormal categories. The training data is learned and fit to a hyperplane by optimising linear coefficients. However, in complex and multi-dimensional problems involving large amounts of data, more advanced techniques such as support vector machines, random forests (applied to T2 map quantification(27)) and DL CNNs are required.(20)

# Applications of machine learning in myocardial infarction cardiovascular magnetic resonance imaging analysis

#### Image segmentation

Manually contouring the borders of the cardiac chambers and myocardium, known as segmentation, is a time-consuming process. In addition, differences in analysis output may still exist between expert readers. In this regard, ML algorithms can help to automate image segmentation and increase productivity, accuracy and reproducibility. This can be achieved through pixel-wise classification or regression-based techniques. Schuster et al showed that fully automated volumetric analysis of MI CMR is feasible and can be equally predictive of major adverse cardiac events when compared with conventional volumetric analysis.(28)

#### Myocardial tissue characterisation

Scar volume from LGE CMR imaging is a prognostic quantitative imaging biomarker.(20) Manual delineation methods of scar volume currently used in routine clinical practice are subjective, time-consuming and labour-intensive. In addition, despite using current thresholding techniques for LGE quantification, accuracy and reproducibility is still affected by intercentre variations, gadolinium kinetics variations and scattered patterns of LGE distribution.(20) A novel, ML-based approach to LGE has been proposed by Fahmy et al(29) using deep CNNs to automatically quantify LV mass and scar volume on LGE images in patients with hypertrophic cardiomyopathy. This could be further extrapolated to quantify infarct size in patients with MI. ML can also be applied to streamline data processing and analysis of cardiac relaxometry.

#### Infarct size/ late gadolinium enhancement

Chen et al proposed an automatic MI segmentation approach based on CNNs to analyse CMR LGE sequences.(30) Their proposal demonstrated promising segmentation results when compared to the intraobserver and interobserver variations in manual segmentation, and to automatic segmentation with Gaussian Mixture Model. Engan et al designed an experimental framework for data exploration which involved computing a very large number of features to describe the characteristics of the regions of interest in the images and found that the addition of texture analysis can improve the discriminative power of scarred and non-scarred myocardium to distinguish between patients with high and low risk of serious ventricular arrhythmias post MI.(31) Kotu et al used pixel intensity-based and underlying texture information-based features to define different cardiac segments such as core and border areas in scarred regions of MI.(32) In another study by Kotu et al, the segmentation of scarred and non-scarred myocardium in MI patients is obtained using different features and feature combinations in a Bayes classifier, with segmentation of scarred myocardium being comparable to manual segmentation in all crossvalidation cases.(33) Larroza et al aimed to differentiate acute from chronic MI using ML techniques and texture features extracted from CMR imaging scans and they were able to conclude that texture analysis can be used for differentiation of acute from chronic MI on LGE sequences, and standard cine sequences in which the infarction is visually imperceptible in most cases.(34) Baessler et al performed a proof-of-concept study whereby stepwise dimension reduction and texture feature selection were performed, enabling the diagnosis of MI on nonenhanced cine images by using LGE imaging as the standard of reference.(35) They showed that texture analysis is feasible and allows for the diagnosis of small and large subacute and chronic ischaemic scars on nonenhanced cine CMR images with high accuracy.(35) In another study by Larroza et al, texture analysis was used to differentiate between infarcted nonviable, viable, and remote segments in MI.(36) Zhang et al demonstrated the use of a DL framework on non-contrast cine CMR that can confirm, detect and delineate transmurality and size of chronic MI.(37) This has positive implications particularly for patients with renal impairment who may be precluded from receiving gadolinium contrast but may require myocardial viability assessment on CMR.

#### Microvascular obstruction/intramyocardial haemorrhage

In another study by Chen et al, they proposed ML-based models to automatically evaluate the severity of MI from physiological, clinical, and paraclinical features.(38) Two types of ML models were investigated for MI assessment: the classification models classify the presence of MI and persistent microvascular obstruction, and the regression models quantify the percentage of infarcted myocardium of patients suspected of having an acute MI in the emergency department.(38) The prediction accuracy for the classification of myocardial state and regression quantification of infarcted myocardium were encouraging. Rosa et al proposed a new automatic method for MI quantification from LGE sequences.(39) Their novel

segmentation approach was devised for accurately detecting hyperenhanced lesions and also MVO areas. It also included a myocardial disease detection step which extended the algorithm for working under healthy scans. Goldfarb et al sought to determine the feasibility and performance of CMR water–fat separation and parametric mapping via DL techniques and demonstrated that myocardial fat deposition in chronic MI and IMH in acute MI could be well visualised with DL strategies.(40)

### <u>T1 mapping</u>

Farrag et al implemented a DL-based method for automated LV segmentation of T1 maps performed using a shortened modified Look-Locker imaging (shMOLLI) sequence by superimposing prior information from cine CMR images in patients with myocardial fibrosis secondary to MI.(41) This helps to circumvent the issue with delineating endocardial-blood pool borders that conventional algorithms face in myocardial segmentation of T1-mapping images due to low signal gradients at the endocardial-blood pool boundary. The accurate delineation of myocardial borders will enable quantification of myocardial fibrosis from native (non-contrast) T1 maps.

### Myocardial perfusion

Perfusion mapping uses AI to provide rapid quantification of myocardial blood perfusion by CMR imaging. In turn, quantitative myocardial blood flow (MBF) provides important prognostic information in patients with suspected CAD in addition to traditional cardiovascular risk factors.(42) Knott et al(42) have shown that in patients with known or suspected CAD, reduced MBF and myocardial perfusion reserve measured automatically inline using AI quantification of CMR perfusion mapping provided robust and independent prediction of major adverse cardiovascular events.

### Radiomics

The ability of ML techniques to handle high-dimensional data has led to the development of radiomics, a novel field in which digital medical images are converted into mineable high-dimensional data by extracting a large number of quantitative imaging features based on mathematical and statistical methods. Within the field of radiomics, texture analysis allow for segmentation, analysis and classification of medical images based on underlying tissue textures as opposed to pure visual image interpretation. The application of radiomics to myocardial tissue characterisation may deliver deeper insights into complex tissue changes in association with pathophysiology of cardiovascular disease.(20)

In the area of MI, radiomics and texture analysis have been applied to the segmentation of myocardial scar and the differentiation between acute and chronic MI. Besides MI, texture analysis and radiomics have also been applied to differentiate between causes of myocardial hypertrophy,(43) prognostication in hypertrophic cardiomyopathy patients with systolic dysfunction,(44) T1 mapping-guided discrimination between hypertensive heart disease and hypertrophic cardiomyopathy,(45) and in the assessment of myocardial inflammation.(46)

Rauseo et al(47) analysed CMR images from the UK Biobank including for patients with history of ischaemic heart disease (IHD) and MI for CMR radiomic signatures and found that shape radiomics such as maximum 2D diameter of the LV and myocardium, myocardial cavity volume and surface area to volume ratio were most relevant in IHD and MI, indicating

the tendency for IHD to result in LV geometry alterations. Avard et al used radiomics analysis and feature identification on non-contrast cine CMR images to accurately detect MI, thus presenting a potential alternative diagnostic method to LGE CMR for MI.(48) Ma et al have shown that combining radiomic signatures of non-contrast-enhanced T1 mapping and T1 values can provide higher diagnostic accuracy for MVO and radiomic signatures can also provide incremental value in predicting LV longitudinal systolic myocardial contractility at six months.(49)

#### Prognostication

ML is well-suited to handle large amounts of clinical information and to find intrinsic structure within this body of information to predict clinical outcomes.(20) Random survival forests technique has been used to identify the top predictors of each outcome measure in the Multi-Ethnic Study of Atherosclerosis (MESA), and CMR-derived LV structure and function were identified as one of the top predictors of incident heart failure.(50) Information maximising component analysis, a supervised feature extraction method, has been used to determine more efficient and sensitive indices of overall remodelling between patients with MI and asymptomatic volunteers from the MESA study.(51) Supervised ML of CMR imaging scans has been used to predict occurrence of cardiac arrhythmia in patients with MI from image-derived scar texture features, size and location of scar.(52)

#### Barriers to implementation

One limitation of ML techniques is the black-box nature of DL algorithms, where it is often unclear what information is used or what interactions between nodes and layers have occurred to derive a certain successful or unsuccessful classification or result.(20) The lack of transparency and explainability could affect user trust which can restrict the use of AI in healthcare. ML models for CMR imaging analysis also need to be robust and portable between scanners, sequences, imaging parameters and centres.(20) Radiomic analysis in particular, is highly dependent on image acquisition parameters that can affect texture and histogram-based intensity values.(47) Heterogenous datasets from different centres should be evaluated to check the validity of proposed ML algorithms on a large scale.(47) Large, publicly available CMR datasets also need to be developed so that different algorithms can be objectively compared for their performance.(20)

#### Governance and quality control

Open source publication of computational processes, codes and datasets can help to mitigate the unpredictable failures of ML algorithms that may occur.(20) Current ML and DL methods can be vulnerable to adversarial attacks that can influence results and render models unsafe for clinical use. To ensure top quality of labelled training data, ground truth must be rigorously reviewed, particularly in clinical reporting where clinicians from different centres may disagree in reporting style and findings.(20)

#### Future applications and directions

Controlled trials are required to evaluate the application of ML methods across multiple centres and varied patient groups. Validation should be performed using data from the same cohort as well as from other cohorts at different centres and using different acquisition devices. For continued advancement of the field, algorithms should be published in open source repositories to enable cross-checking, benchmarking, replication and improvement by international groups. In addition, although large cohort data sets have been used for ML training, these applications must be extended with care to specific patient groups with various pathologies and with fair representation so that variations between age, sex and ethnicities can also be accounted for.(20)

#### Conclusion

AI, ML and more specifically DL can improve efficiency, reproducibility, precision and accuracy in the assessment of important prognostic imaging biomarkers in MI CMR scans through the development of automated CMR analysis strategies. Global collaboration through open-source publication of codes and datasets will help to further advance the field and improve governance, safety and quality control through knowledge sharing. Future directions include the incorporation of automated analysis within clinical trials that assess clinical outcomes, and the extension of existing ML applications to heterogenous patient cohorts.

#### Declarations of interest

Steffen E Petersen (SEP) provides consultancy to Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada. All other authors declare no conflicts of interest.

#### **Acknowledgments**

Jun Hua Chong (JHC) has been supported by the Singapore Ministry of Health's National Medical Research Council Research Training Fellowship (FLWSHP19may-0013), National Medical Research Council Collaborative Centre Grant Seed Funding (NHCS-CGSF/2019/002) and New Toyo Cardiovascular Research and Education Fund (07/FY2021/EX(SL)/77-A131). SEP acknowledges support from the National Institute for Health Research (NIHR) Biomedical Research Centre at Barts. SEP has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825903 (euCanSHare project). SEP acknowledges support from and from the "SmartHeart" EPSRC programme grant (www.nihr.ac.uk; EP/P001009/1). SEP and Musa Abdulkareem (MA) also acknowledge support from the CAP-AI programme, London's first AI enabling programme focused on stimulating growth in the capital's AI Sector. CAP-AI is led by Capital Enterprise in partnership with Barts Health NHS Trust and Digital Catapult and is funded by the European Regional Development Fund and Barts Charity. This article is supported by the London Medical Imaging and Artificial Intelligence Centre for Value Based Healthcare (AI4VBH), which is funded from the Data to Early Diagnosis and Precision Medicine strand of the government's Industrial Strategy Challenge Fund, managed and

delivered by Innovate UK on behalf of UK Research and Innovation (UKRI). Views expressed are those of the authors and not necessarily those of the AI4VBH Consortium members, the NHS, Innovate UK, or UKRI. This work was supported by Health Data Research UK, an initiative funded by UK Research and Innovation, Department of Health and Social Care (England) and the devolved administrations, and leading medical research charities.

### References

- 1. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018 Jan;39(2):119–77.
- 2. Leiner T, Bogaert J, Friedrich MG, Mohiaddin R, Muthurangu V, Myerson S, et al. SCMR Position Paper (2020) on clinical indications for cardiovascular magnetic resonance. J Cardiovasc Magn Reson [Internet]. 2020;22(1):76. Available from: https://doi.org/10.1186/s12968-020-00682-4
- Schulz-Menger J, Bluemke DA, Bremerich J, Flamm SD, Fogel MA, Friedrich MG, et al. Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) Board of Trustees Task Force on Standardized Post Processing. J Cardiovasc Magn Reson [Internet]. 2013;15(1):35. Available from: https://doi.org/10.1186/1532-429X-15-35
- 4. Kim HW, Farzaneh-Far A, Kim RJ. Cardiovascular magnetic resonance in patients with myocardial infarction: current and emerging applications. J Am Coll Cardiol. 2009 Dec;55(1):1–16.
- 5. Wagner A, Mahrholdt H, Holly TA, Elliott MD, Regenfus M, Parker M, et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. Lancet (London, England). 2003 Feb;361(9355):374–9.
- 6. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2\* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson. 2017 Oct;19(1):75.
- 7. Roes SD, Kelle S, Kaandorp TAM, Kokocinski T, Poldermans D, Lamb HJ, et al. Comparison of myocardial infarct size assessed with contrast-enhanced magnetic resonance imaging and left ventricular function and volumes to predict mortality in patients with healed myocardial infarction. Am J Cardiol. 2007 Sep;100(6):930–6.
- 8. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation. 1987 Jul;76(1):44–51.
- 9. Bulluck H, Dharmakumar R, Arai AE, Berry C, Hausenloy DJ. Cardiovascular

Magnetic Resonance in Acute ST-Segment-Elevation Myocardial Infarction: Recent Advances, Controversies, and Future Directions. Circulation. 2018 May;137(18):1949–64.

- Stone GW, Selker HP, Thiele H, Patel MR, Udelson JE, Ohman EM, et al. Relationship Between Infarct Size and Outcomes Following Primary PCI: Patient-Level Analysis From 10 Randomized Trials. J Am Coll Cardiol. 2016 Apr;67(14):1674–83.
- Carrick D, Haig C, Ahmed N, McEntegart M, Petrie MC, Eteiba H, et al. Myocardial Hemorrhage After Acute Reperfused ST-Segment-Elevation Myocardial Infarction: Relation to Microvascular Obstruction and Prognostic Significance. Circ Cardiovasc Imaging. 2016 Jan;9(1):e004148.
- 12. Hamirani YS, Wong A, Kramer CM, Salerno M. Effect of microvascular obstruction and intramyocardial hemorrhage by CMR on LV remodeling and outcomes after myocardial infarction: a systematic review and meta-analysis. JACC Cardiovasc Imaging. 2014 Sep;7(9):940–52.
- 13. Eitel I, de Waha S, Wöhrle J, Fuernau G, Lurz P, Pauschinger M, et al. Comprehensive prognosis assessment by CMR imaging after ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2014 Sep;64(12):1217–26.
- 14. Bøtker HE, Kaltoft AK, Pedersen SF, Kim WY. Measuring myocardial salvage. Cardiovasc Res. 2012 May;94(2):266–75.
- 15. Bulluck H, Hammond-Haley M, Fontana M, Knight DS, Sirker A, Herrey AS, et al. Quantification of both the area-at-risk and acute myocardial infarct size in STsegment elevation myocardial infarction using T1-mapping. J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson. 2017 Aug;19(1):57.
- 16. Verhaert D, Thavendiranathan P, Giri S, Mihai G, Rajagopalan S, Simonetti OP, et al. Direct T2 quantification of myocardial edema in acute ischemic injury. JACC Cardiovasc Imaging. 2011 Mar;4(3):269–78.
- 17. Bulluck H, White SK, Rosmini S, Bhuva A, Treibel TA, Fontana M, et al. T1 mapping and T2 mapping at 3T for quantifying the area-at-risk in reperfused STEMI patients. J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson. 2015 Aug;17(1):73.
- Bulluck H, White SK, Fröhlich GM, Casson SG, O'Meara C, Newton A, et al. Quantifying the Area at Risk in Reperfused ST-Segment-Elevation Myocardial Infarction Patients Using Hybrid Cardiac Positron Emission Tomography-Magnetic Resonance Imaging. Circ Cardiovasc Imaging. 2016 Mar;9(3):e003900.
- Dall'Armellina E, Karia N, Lindsay AC, Karamitsos TD, Ferreira V, Robson MD, et al. Dynamic changes of edema and late gadolinium enhancement after acute myocardial infarction and their relationship to functional recovery and salvage index. Circ Cardiovasc Imaging. 2011 May;4(3):228–36.
- Leiner T, Rueckert D, Suinesiaputra A, Baeßler B, Nezafat R, Išgum I, et al. Machine learning in cardiovascular magnetic resonance: basic concepts and applications. J Cardiovasc Magn Reson [Internet]. 2019;21(1):61. Available from: https://doi.org/10.1186/s12968-019-0575-y
- 21. Hoerl AE, Kennard RW. Ridge Regression: Biased Estimation for Nonorthogonal

Problems. Technometrics [Internet]. 1970 Feb 1;12(1):55–67. Available from: https://www.tandfonline.com/doi/abs/10.1080/00401706.1970.10488634

- 22. Schölkopf B. The Kernel Trick for Distances. In: Proceedings of the 13th International Conference on Neural Information Processing Systems. Cambridge, MA, USA: MIT Press; 2000. p. 283–289. (NIPS'00).
- Quinlan JR. Simplifying decision trees. Int J Man Mach Stud [Internet]. 1987;27(3):221–34. Available from: https://www.sciencedirect.com/science/article/pii/S0020737387800536
- 24. Breiman L. Bias, variance, and arcing classifiers. Tech. Rep. 460, Statistics Department, University of California, Berkeley ...; 1996.
- Izenman AJ. Linear Discriminant Analysis BT Modern Multivariate Statistical Techniques: Regression, Classification, and Manifold Learning. In: Izenman AJ, editor. New York, NY: Springer New York; 2008. p. 237–80. Available from: https://doi.org/10.1007/978-0-387-78189-1\_8
- 26. Maclin R, Opitz DW. Popular Ensemble Methods: An Empirical Study. J Artif Intell Res. 1999;11:169–98.
- 27. Baeßler B, Schaarschmidt F, Dick A, Stehning C, Schnackenburg B, Michels G, et al. Mapping tissue inhomogeneity in acute myocarditis: a novel analytical approach to quantitative myocardial edema imaging by T2-mapping. J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson. 2015 Dec;17:115.
- 28. Schuster A, Lange T, Backhaus SJ, Strohmeyer C, Boom PC, Matz J, et al. Fully Automated Cardiac Assessment for Diagnostic and Prognostic Stratification Following Myocardial Infarction. J Am Heart Assoc. 2020 Sep;9(18):e016612.
- Fahmy AS, Rausch J, Neisius U, Chan RH, Maron MS, Appelbaum E, et al. Automated Cardiac MR Scar Quantification in Hypertrophic Cardiomyopathy Using Deep Convolutional Neural Networks. Vol. 11, JACC. Cardiovascular imaging. 2018. p. 1917–8.
- 30. Chen Z, Lalande A, Salomon M, Decourselle T, Pommier T, Qayyum A, et al. Automatic deep learning-based myocardial infarction segmentation from delayed enhancement MRI. Comput Med Imaging Graph [Internet]. 2022;95:102014. Available from: https://www.sciencedirect.com/science/article/pii/S0895611121001634
- 31. Engan K, Eftestol T, Orn S, Kvaloy JT, Woie L. Exploratory data analysis of image texture and statistical features on myocardium and infarction areas in cardiac magnetic resonance images. Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Int Conf. 2010;2010:5728–31.
- 32. Kotu LP, Engan K, Skretting K, Måløy F, Orn S, Woie L, et al. Probability mapping of scarred myocardium using texture and intensity features in CMR images. Biomed Eng Online. 2013 Sep;12:91.
- Kotu LP, Engan K, Skretting K, Ørn S, Woie L, Eftestøl T. Segmentation of Scarred Myocardium in Cardiac Magnetic Resonance Images. Tomanek B, Waiter G, editors. ISRN Biomed Imaging [Internet]. 2013;2013:504594. Available from: https://doi.org/10.1155/2013/504594

- 34. Larroza A, Materka A, López-Lereu MP, Monmeneu J V, Bodí V, Moratal D. Differentiation between acute and chronic myocardial infarction by means of texture analysis of late gadolinium enhancement and cine cardiac magnetic resonance imaging. Eur J Radiol. 2017 Jul;92:78–83.
- 35. Baessler B, Mannil M, Oebel S, Maintz D, Alkadhi H, Manka R. Subacute and Chronic Left Ventricular Myocardial Scar: Accuracy of Texture Analysis on Nonenhanced Cine MR Images. Radiology. 2018 Jan;286(1):103–12.
- 36. Larroza A, López-Lereu MP, Monmeneu J V, Gavara J, Chorro FJ, Bodí V, et al. Texture analysis of cardiac cine magnetic resonance imaging to detect nonviable segments in patients with chronic myocardial infarction. Med Phys. 2018 Apr;45(4):1471–80.
- Zhang N, Yang G, Gao Z, Xu C, Zhang Y, Shi R, et al. Deep Learning for Diagnosis of Chronic Myocardial Infarction on Nonenhanced Cardiac Cine MRI. Radiology. 2019 Jun;291(3):606–17.
- Chen Z, Shi J, Pommier T, Cottin Y, Salomon M, Decourselle T, et al. Prediction of Myocardial Infarction From Patient Features With Machine Learning. Front Cardiovasc Med [Internet]. 2022;9. Available from: https://www.frontiersin.org/article/10.3389/fcvm.2022.754609
- 39. de la Rosa E, Sidibé D, Decourselle T, Leclercq T, Cochet A, Lalande A. Myocardial Infarction Quantification from Late Gadolinium Enhancement MRI Using Top-Hat Transforms and Neural Networks. Vol. 14, Algorithms . 2021.
- Goldfarb JW, Craft J, Cao JJ. Water–fat separation and parameter mapping in cardiac MRI via deep learning with a convolutional neural network. J Magn Reson Imaging [Internet]. 2019 Aug 1;50(2):655–65. Available from: https://doi.org/10.1002/jmri.26658
- 41. Farrag NA, M.D. JAW, Ukwatta E. Semi-automated myocardial segmentation in native T1-mapping CMR using deformable non-rigid registration of CINE images. In: ProcSPIE [Internet]. 2019. Available from: https://doi.org/10.1117/12.2513054
- 42. Knott KD, Seraphim A, Augusto JB, Xue H, Chacko L, Aung N, et al. The Prognostic Significance of Quantitative Myocardial Perfusion: An Artificial Intelligence-Based Approach Using Perfusion Mapping. Circulation. 2020 Apr;141(16):1282–91.
- 43. Schofield R, Ganeshan B, Kozor R, Nasis A, Endozo R, Groves A, et al. CMR myocardial texture analysis tracks different etiologies of left ventricular hypertrophy. J Cardiovasc Magn Reson [Internet]. 2016;18(1):O82. Available from: https://doi.org/10.1186/1532-429X-18-S1-O82
- 44. Cheng S, Fang M, Cui C, Chen X, Yin G, Prasad SK, et al. LGE-CMR-derived texture features reflect poor prognosis in hypertrophic cardiomyopathy patients with systolic dysfunction: preliminary results. Eur Radiol. 2018 Nov;28(11):4615–24.
- 45. Neisius U, El-Rewaidy H, Nakamori S, Rodriguez J, Manning WJ, Nezafat R. Radiomic Analysis of Myocardial Native T(1) Imaging Discriminates Between Hypertensive Heart Disease and Hypertrophic Cardiomyopathy. JACC Cardiovasc Imaging. 2019 Oct;12(10):1946–54.
- 46. Baessler B, Luecke C, Lurz J, Klingel K, von Roeder M, de Waha S, et al. Cardiac

MRI Texture Analysis of T1 and T2 Maps in Patients with Infarctlike Acute Myocarditis. Radiology [Internet]. 2018 Aug 7;289(2):357–65. Available from: https://doi.org/10.1148/radiol.2018180411

- 47. Rauseo E, Izquierdo Morcillo C, Raisi-Estabragh Z, Gkontra P, Aung N, Lekadir K, et al. New Imaging Signatures of Cardiac Alterations in Ischaemic Heart Disease and Cerebrovascular Disease Using CMR Radiomics. Front Cardiovasc Med [Internet]. 2021;8. Available from: https://www.frontiersin.org/article/10.3389/fcvm.2021.716577
- Avard E, Shiri I, Hajianfar G, Abdollahi H, Kalantari KR, Houshmand G, et al. Noncontrast Cine Cardiac Magnetic Resonance image radiomics features and machine learning algorithms for myocardial infarction detection. Comput Biol Med [Internet]. 2022;141:105145. Available from: https://www.sciencedirect.com/science/article/pii/S0010482521009392
- Ma Q, Ma Y, Yu T, Sun Z, Hou Y. Radiomics of Non-Contrast-Enhanced T1 Mapping: Diagnostic and Predictive Performance for Myocardial Injury in Acute ST-Segment-Elevation Myocardial Infarction. Korean J Radiol [Internet]. 2021 Apr;22(4):535–46. Available from: https://doi.org/10.3348/kjr.2019.0969
- 50. Ambale-Venkatesh B, Yang X, Wu CO, Liu K, Hundley WG, McClelland R, et al. Cardiovascular Event Prediction by Machine Learning: The Multi-Ethnic Study of Atherosclerosis. Circ Res. 2017 Oct;121(9):1092–101.
- 51. Zhang X, Ambale-Venkatesh B, Bluemke DA, Cowan BR, Finn JP, Kadish AH, et al. Information maximizing component analysis of left ventricular remodeling due to myocardial infarction. J Transl Med [Internet]. 2015;13(1):343. Available from: https://doi.org/10.1186/s12967-015-0709-4
- 52. Kotu LP, Engan K, Borhani R, Katsaggelos AK, Ørn S, Woie L, et al. Cardiac magnetic resonance image-based classification of the risk of arrhythmias in post-myocardial infarction patients. Artif Intell Med. 2015 Jul;64(3):205–15.
- 53. Carter KM, Raich R, Finn WG, Hero AO. Information Preserving Component Analysis: Data Projections for Flow Cytometry Analysis. IEEE J Sel Top Signal Process. 2009;3(1):148–58.

Table 1. Summary of studies utilising artificial intelligence-enabled analysis methods on cardiovascular magnetic resonance imaging scans of myocardial infarction.

Research	Year of	Imaging	Results	Machine learning
group	publication	biomarker		method(s)
Schuster	2020	Volumetric	Fully automated	Use of AI-based
et al(28)		analysis and	volumetric analysis of MI	software
		infarct size	CMR is feasible and can	(Manufacturer's
		analysis	be equally predictive of	undisclosed DL-
			major adverse cardiac	based model)
			events when compared	

			with conventional volumetric analysis	
Chen et al(30)	2022	MI segmentation	Demonstrated promising segmentation results when compared to the intraobserver and interobserver variations in manual segmentation, and to automatic segmentation with Gaussian Mixture Model.	CNNs (versus Gaussian Mixture Model)
Engan et al(31)	2010	Scarred and non-scarred myocardium	Addition of texture analysis can improve discriminative power of scarred and non-scarred myocardium to distinguish between patients with high and low risk of serious ventricular arrhythmias post-MI	Maximum likelihood estimation with Bayes classifiers
Kotu et al(32)	2013	Core and border areas in scarred regions of MI	Pixel intensity-based and underlying texture information-based features were used to define different cardiac segments such as core and border areas in scarred regions of MI.	Probability function based on Bayes rule
Kotu et al(33)	2013	Segmentation of scarred and non-scarred myocardium in MI	Segmentation of scarred and non-scarred myocardium in MI patients obtained using different features and feature combinations in a Bayes classifier, with segmentation of scarred myocardium being comparable to manual segmentation in all cross- validation cases	Maximum likelihood estimation with Bayes classifiers
Larroza et al(34)	2017	Texture features extracted from	Demonstrated that texture analysis can be used for differentiation of acute	Three ML methods: Random forest, support

		infarcted area on LGE CMR images, and the entire myocardium on cine CMR.	from chronic MI on LGE sequences and standard cine sequences	vector machine (SVM) with Gaussian Kernel, and SVM with polynomial kernel.
Baessler et al(35)	2018	Subacute and chronic ischaemic scar	Enabled the diagnosis of MI on nonenhanced cine images by using LGE imaging as the standard of reference. Method involved stepwise dimension reduction and texture feature selection	Multiple logistic regression models
Larroza et al(36)	2018	Infarcted nonviable, viable and remote segments	Texture analysis was used to differentiate between infarcted nonviable, viable, and remote segments in MI	SVM
Zhang et al(37)	2019	Transmurality and size of chronic MI	DL framework was used on non-contrast cine CMR to confirm, detect and delineate transmurality and size of chronic MI. Also uses computer vision dense (optical) flow method.	Three DL methods: CNN, long short-term memory (LSTM), and stacked auto- encoder
Chen et al(38)	2022	Presence of MI and MVO and quantification of infarcted myocardium	Prediction accuracy for the classification of myocardial state and regression quantification of infarcted myocardium were encouraging	Methods used for regression: linear regression, support vector regression, decision tree regression, random forest, multilayer perceptron, gradient boosting, XGBoost, light gradient boosting, and ensemble method. Methods used for classification:

				random forests and SVM with linear kernel function.
Rosa et al(39)	2021	Hyperenhanced lesions and also MVO areas.	Novel segmentation approach was devised for accurately detecting hyperenhanced lesions and also MVO areas. Also uses computer vision Otsu's method for image processing.	CNN, principal component analysis, and SVM
Goldfarb et al(40)	2019	CMR water-fat separation and parametric mapping	Myocardial fat deposition in chronic MI and IMH in acute MI could be well visualised with DL strategies	CNN
Farrag et al(41)	2019	Automated LV segmentation of T1 maps	DL-based method implemented for automated LV segmentation of T1 maps performed using a shortened modified Look- Locker imaging (shMOLLI) sequence by superimposing prior information from cine CMR images in patients with myocardial fibrosis secondary to MI	Modality independent neighbourhood descriptor (MIND)
Knott et al(42)	2020	MBF and myocardial perfusion reserve	In patients with known or suspected CAD, reduced MBF and myocardial perfusion reserve measured automatically inline using AI quantification of CMR perfusion mapping provided robust and independent prediction of major adverse cardiovascular events	CNN

Rauseo et al(47)	2021	Maximum 2D diameter of the LV and myocardium, myocardial cavity volume and surface area to volume ratio	Shape radiomics such as maximum 2D diameter of the LV and myocardium, myocardial cavity volume and surface area to volume ratio were most relevant in IHD and MI, indicating the tendency for IHD to result in LV geometry alterations	SVM and random forest (RF)
Avard et al(48)	2022	Radiomics analysis and feature identification on non-contrast cine CMR images to accurately detect MI	Radiomics analysis and feature identification was used to accurately detect MI in non-contrast cine CMR images, presenting a potential alternative diagnostic method to LGE CMR for MI	SVM, RF, Extra Tree, Logistic Regression, Linear Discriminant Analysis, Quadratic Discriminant Analysis, AdaBoost, k- nearest neighbor (k-NN), Naïve Bayes, Multilayer Perceptron
Ma et al(49)	2021	Radiomic signatures of non-contrast- enhanced T1 mapping and T1 values	Combining radiomic signatures of non-contrast- enhanced T1 mapping and T1 values can provide higher diagnostic accuracy for MVO and radiomic signatures can also provide incremental value in predicting LV longitudinal systolic myocardial contractility at six months	LASSO regression analysis
Zhang et al(51)	2015	LV remodelling index post-MI	IMCA enables better characterisation of global remodelling than linear discriminant analysis, and can be used to quantify progression of disease and the effect of treatment	Linear discriminant analysis, principal component analysis, and information maximising component analysis (i.e. Information preserving

				component analysis)(53)
Kotu et al(52)	2015	Size, location, and textural information concerning the scarred myocardium	Texture features based on scar gradient and local binary patterns along with localisation features demonstrated good discriminative power when distinguishing low- risk versus high-risk patients for developing arrhythmias post-MI	k-NN and SVM

Table legend: MI – myocardial infarction; CMR – cardiovascular magnetic resonance; AI – artificial intelligence; CNN – convolutional neural network; LGE – late gadolinium enhancement; DL – deep learning; MVO – microvascular obstruction; ML – machine learning; IMH – intramyocardial haemorrhage; LV – left ventricle; MBF – myocardial blood flow; CAD – coronary artery disease; IHD – ischaemic heart disease; IMCA - information maximising component analysis.

## Utility of AI/DL-based strategies in analysis of CMR MI imaging biomarkers

#### **Remote myocardium**

- Texture analysis to differentiate between infarcted non-viable. viable and remote segments
- MBF and myocardial perfusion reserve in known or suspected CAD

## Hypointense core (MVO or IMH)

- Novel segmentation approach for detecting hyperenhanced lesions and MVO
- · DL strategies to delineate myocardial fat deposition and IMH from analysis of CMR water-fat separation and parametric mapping



Figure 1. Utility of artificial intelligence/deep learning-based strategies in analysis of cardiovascular magnetic resonance myocardial infarction imaging biomarkers

Figure legend: MI – myocardial infarction; CMR – cardiovascular magnetic resonance; AI – artificial intelligence; DL – deep learning; MVO – microvascular obstruction; ML – machine learning; IMH – intramyocardial haemorrhage; LV – left ventricle; MBF – myocardial blood flow; CAD – coronary artery disease; IHD – ischaemic heart disease; MACE – major adverse cardiovascular events; IHD – ischaemic heart disease.

# Late gadolinium

- Automatic segmentation of MI
- Texture analysis of scarred and
- Pixel intensity-based and texturebased features to define core and
- Diagnosis of MI on non-enhanced
- Delineation of transmurality on
- Automated LV segmentation of T1 maps