Deep learning applications in coronary anatomy imaging: a systematic review and meta-analysis

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Background: The application of deep learning on medical imaging is growing in prevalence in the recent literature. One of the most studied areas is coronary artery disease (CAD). Imaging of coronary artery anatomy is fundamental, which has led to a high number of publications describing a variety of techniques. The aim of this systematic review is to review the evidence behind the accuracy of deep learning applications in coronary anatomy imaging.

Methods: The search for the relevant studies, which applied deep learning on coronary anatomy imaging, was performed in a systematic approach on MEDLINE and EMBASE databases, followed by reviewing of abstracts and full texts. The data from the final studies was retrieved using data extraction forms. A meta-analysis was performed on a subgroup of studies, which looked at fractional flow reserve (FFR) prediction. Heterogeneity was tested using tau^2, I^2 and Q tests. Finally, a risk of bias was performed using Quality Assessment of Diagnostic Accuracy Studies (QUADAS) approach.

Results: A total of 81 studies met the inclusion criteria. The most common imaging modality was coronary computed tomography angiography (CCTA) (58%) and the most common deep learning method was convolutional neural network (CNN) (52%). The majority of studies demonstrated good performance metrics. The most common outputs were focused on coronary artery segmentation, clinical outcome prediction, coronary calcium quantification and FFR prediction, and most studies reported area under the curve (AUC) of ≥80%. The pooled diagnostic odds ratio (DOR) derived from 8 studies looking at FFR prediction using CCTA was 12.5 using the Mantel-Haenszel (MH) method. There was no significant heterogeneity amongst studies according to Q test (P=0.2496).

Conclusions: Deep learning has been used in many applications on coronary anatomy imaging, most of which are yet to be externally validated and prepared for clinical use. The performance of deep learning, especially CNN models, proved to be powerful and some applications have already translated into medical practice, such as computed tomography (CT)-FFR. These applications have the potential to translate technology into better care of CAD patients.

Keywords: Deep learning; coronary anatomy; atherosclerosis; coronary computed tomography angiography (CCTA); coronary artery disease (CAD)

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Introduction

Background

Coronary artery disease (CAD) is considered a leading cause of death and hospitalisation in high-income countries, and worldwide (1). The progressive nature of coronary atherosclerosis is the main underlying pathological process. Therefore, it is essential to have timely diagnosis of CAD to aid the management of patients and reduce both morbidity and mortality.

The last two decades have witnessed significant advancements in CAD imaging, from functional assessment of coronary artery stenoses and how they impact on the myocardium at stress and rest, using cardiac magnetic resonance (CMR), myocardial perfusion scintigraphy (MPS), and echocardiography, to anatomical assessment by means of coronary computed tomography angiography (CCTA) and invasive X-rays coronary angiography.

Computer vision technology on the other hand is going through an exciting era following the revolution of deep learning and artificial intelligence (AI) algorithms. CAD imaging is one of the key applications which has been targeted by many computer vision experts and deep learning practitioners.

Rationale and objectives

There has been an explosion in the number of deep learning publications in CAD over the recent years with a focus on atherosclerosis and coronary anatomy imaging. The wide range of methodology presented in the recent literature opened the door for applications in various coronary artery imaging modalities.

The mounting volume of new literature has left clinicians with a two-fold challenge: first of how to deal with increasing volume of new information on CAD diagnosis, prognosis, and risk stratification, and second of how far can we trust the evidence of machine learning and deep learning algorithms to make decisions on patients' care.

This review aims to unravel this challenge by summarising the new information we gained so far in this field, evaluating the performance of the presented deep learning algorithms, and drawing some conclusions on potential meaningful applications. We present the following article in accordance with the PRISMA reporting checklist (available at https://jmai.amegroups.com/article/view/10.21037/jmai-22-36/rc).

Highlight box

Key findings
- Deep learning has important applications in coronary anatomy imaging.
- CT-FFR is an example which has translated into clinical practice and patients' care.
- CNNs have been the most powerful in recent literature.

What is known and what is new?
- Coronary anatomy imaging is mainly assessed by human experts.
- Deep learning has shown a high performance in coronary anatomy interpretation, prediction, and improving patient care and safety.

What is the implication, and what should change now?
- Research in deep learning for coronary anatomy imaging is making significant advancements.
- Successful deep learning applications will require clinical validation.

Methods

Design

This review follows the Cochrane Review structure of diagnostic test accuracy (DTA) (2). The umbrella protocol for this systematic review is registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42020204164), and reported according to PRISMA guidelines. All searching activities were performed by two independent reviewers (EA and UD), with divergences solved after consensus.

The PICO approach was used to define the main review question:

❖ Population: adults' cohort with suspected or known CAD;
❖ Intervention: deep learning applications in coronary atherosclerosis imaging;
❖ Comparison: comparison with conventional coronary atherosclerosis imaging;
❖ Outcome: improve test accuracy and patient care.

Selection criteria

Without restrictions on minimal sample sizes or recruitment process, both prospective and retrospective studies were included. The included studies had participants with known or suspected CAD who had atherosclerosis imaging (invasive and non-invasive) with the application of deep learning technology, and compared with the gold standard (reference) test used in clinical practice.

Competitions presented in conferences on deep learning techniques, such as at the Medical Image Computing and Computer Assisted Intervention (MICCAI) conference, animal studies, and simulation studies were not included due to ambiguity in their direct relation to patient care. Studies which used atherosclerosis data as a target for outcome prediction were excluded, as were studies, which focused on clinical data and imaging reports rather than imaging data for prediction. Studies, which used deep learning software with no details on the deep learning architecture were also excluded. Fusion imaging studies were not part of this review, and studies of automated coronary anatomy and atherosclerosis quantification, which relied mainly on hand crafted or non-learning algorithms were not included.

For fractional flow reserve (FFR) derived from CCTA using deep learning, only the original publications were included in this review, all subsequent publications, which used the same algorithms for different clinical applications were considered external validation papers and were not included in this review.

Search procedure

MEDLINE (with PubMed extension) and EMBASE using Ovid search engine was conducted to search the published literature. Yale Mesh Analyzer was used to include all possible Medline Subject Headings (MeSH) terms, after identifying two studies manually on MEDLINE database with focus on deep learning and CAD atherosclerosis imaging modalities. The PMIDs for those papers were extracted and inserted into the analyser, these produced Mesh terms to guide the systematic search. Truncation has been used in imaging term: [‘coronar*’], [‘myocardia*’], [‘atherosclero*’], [‘isch?mi*’], and [‘calci*’]. Plain terms were used for [‘machine learning’], [‘deep learning’], [‘artificial intelligence’], [‘neural networks’], [‘unsupervised learning’], [‘supervised learning’], [‘semi-supervised learning’], [‘heart’], [‘plaque’], and [‘stenosis’]. The search included all records from database inception until 21st of October 2020 with no language constraints. Data was collected by EA and UD. Full Ovid search strategy and output is shown in https://cdn.amegroups.cn/static/public/jmai-22-36-1.pdf. Due to reports of missing relevant studies and inconsistency using methodology search filters (2), this approach has not been used.

Search results

Search results yielded 81 studies to be used for the systematic review and only a subset of 8 studies with unified defined outcomes were used for meta-analysis. Search results are shown in *Figure 1*.

Data extraction

The summary of input data, which were extracted from each study are reported below:

(I) First author’s surname;
(II) Year of publication;
(III) Total number of participants (images if not available);
(IV) Imaging modality used for deep learning;
(V) Index test;
(VI) Reference test;
(VII) Deep learning techniques;
(VIII) External validation;
(IX) Model performance metrics.

Assessment of risk of bias

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool was used to assess the risk of bias. Five main fields were assessed using a modified version:

(I) Patient selection: randomly selected patients from a population meeting the inclusion criteria is considered a high-quality study;
(II) Index test: including a comparator test is expected in a high-quality diagnostic test study;
(III) Reference test: a gold standard test for validation is mandatory in all high-quality diagnostic test studies;
(IV) Index test results blinded: the results of the comparator test are expected to be blinded to the deep learning arm in a high-quality study;
(V) Reference test results blinded: the results of the gold standard test are expected to be blinded to the deep learning arm in a high-quality study.

Statistical analysis

The performance of deep learning models was measured with various metrics including sensitivity, specificity, area under the curve (AUC), precision, recall, F1 score, Dice coefficient, Jaccard coefficient, and correlation. Those metrics were described quantitatively.

Data were reported as count or percentages. The pooled values of some of the reported diagnostic accuracy after the

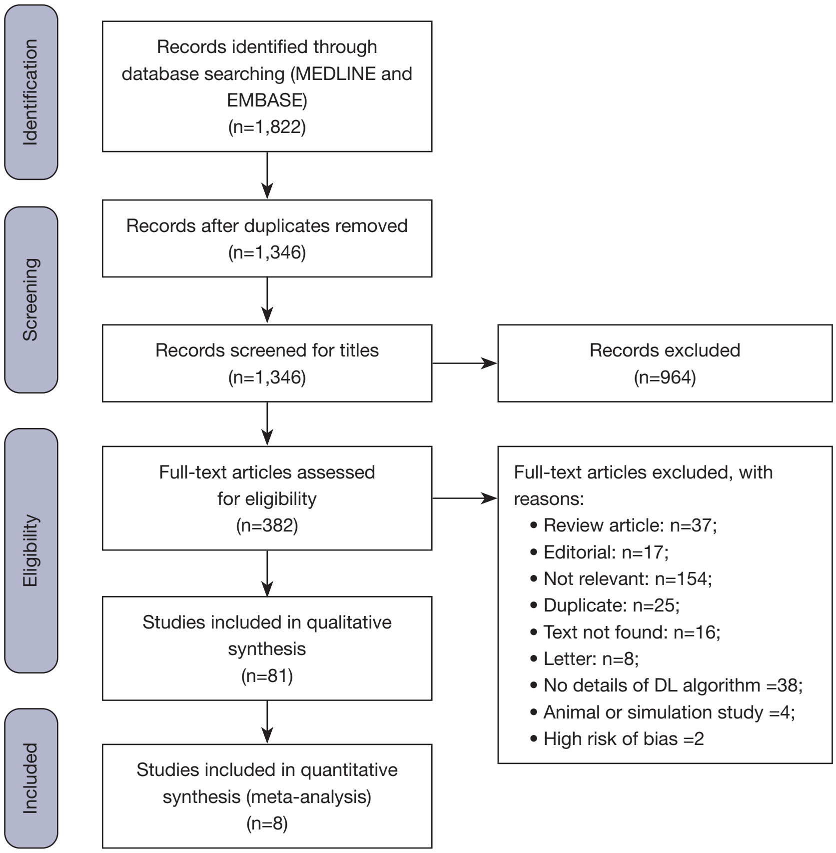

Figure 1 PRISMA flow diagram showing the results of systematic search strategy. DL, deep learning.

application of deep learning models, which were part of the meta-analysis, were visualised by forest plots.

A confusion matrix was produced for each of the included studies in meta-analysis given that most studies did not report the true negative (TN), true positive (TP), false negative (FN), and false positive (FP) values. This was calculated by taking sample size (S) to calculate FN from sensitivity, and FP from specificity. The TN and TP were then calculated from total sample size S.

Meta-analysis was performed on studies, which reported the same outputs with the corresponding sensitivity and specificity. Since pooling sensitivities or specificities can be misleading, the diagnostic odds ratio (DOR) approach is taken to calculate the pooled diagnostic performance. The fixed effect case of Mantel-Haenszel (MH) method is used.

Heterogeneity was examined using tau^2, I^2 and Q tests. P value of less than 0.05 was considered statistically significant.

All statistical analysis was performed using RStudio software version 1.4.1106 using R 4.0.4 programming language.

Results

Characteristics of studies

The final number of studies included in this systematic review was 81, all published over 6 years between 2015 and 2020, which indicates the recency of this topic.

Details of first author, year of publication, sample size, deep learning and machine learning techniques, index test (comparator) and reference test (gold standard) are shown in *Table 1*.

The most popular imaging modality in deep learning application was CCTA (58%), as shown in *Figure 2*. However, invasive coronary angiography has gained more interest in recent years, along with invasive coronary intravascular imaging [optical coherence tomography (OCT) and intravascular ultrasound (IVUS)], which have been a focus for deep learning applications in recent years. Both

Table 1 List of all relevant studies for coronary anatomy imaging included in this systematic review

First author	Year	Model output	Sample size	Imaging modality	Model	Index test	Reference test	External validation
Rodrigues *et al.* (3)	2016	Pericardial and mediastinal fat classification	20	CCTA	RF	Manual feature extraction algorithms	Expert reader	No
Kang *et al.* (4)	2015	Coronary stenosis classification	42	CCTA	SVM	Expert reader	Invasive coronary angiography	No
Araki *et al.* (5)	2016	Coronary plaque calcification	15	IVUS	SVM	NA	cIMT	No
Itu *et al.* (6)	2016	FFR prediction	87	CCTA	MLP	Computational fluid dynamics CT-FFR	Invasive FFR	Yes
Wolterink *et al.* (7)	2016	CAC quantification	250	CCTA	CNN	NA	Expert reader	No
Su *et al.* (8)	2017	Media adventitia border detection	4	IVUS	MLP	NA	Expert reader	No
Yong *et al.* (9)	2017	Coronary lumen segmentation	64	OCT	CNN	NA	Expert reader	No
Xu *et al.* (10)	2017	Coronary plaque classification	18	OCT	CNN and SVM	NA	Expert reader	No
Zreik *et al.* (11)	2019	Coronary plaque classification	163	CCTA	RNN	NA	Expert reader	No
Zreik *et al.* (12)	2018	LV segmentation for coronary stenosis significance classification	156	CCTA	CNN + SVM	NA	Invasive FFR	No
Kolluru *et al.* (13)	2018	Coronary plaque classification	48	OCT	CNN	NA	Expert reader	No
Zhang *et al.* (14)	2018	Coronary plaque classification	61	IVUS	SVM	NA	Expert reader	No
Oh *et al.* (15)	2018	Lipid core plaque detection	116	IVUS	CNN	NA	Expert reader	No
van Rosendael *et al.* (16)	2018	Clinical outcome prediction	8,844	CCTA	Boosted ensemble algorithm	Conventional clinical risk scores	Clinical outcomes	No
Stuckey *et al.* (17)	2018	CAD detection	606	cPSTA	Elastic net	NA	Invasive coronary angiography	No
Lessmann *et al.* (18)	2018	CAC detection	1,744	CCTA	CNN	NA	Expert reader	No
Šprem *et al.* (19)	2018	Motion artefact detection in CACS	585	CCTA	CNN	NA	Conventional CACS	No
Hae *et al.* (20)	2018	Prediction of myocardium subtended by coronary stenosis	932	CCTA	SVM	NA	Invasive coronary angiography	Yes
Dey *et al.* (21)	2018	FFR prediction	254	CCTA	Boosted ensemble algorithm	Conventional CCTA	Invasive FFR	No
van Hamersvelt *et al.* (22)	2019	LV segmentation for coronary stenosis significance classification	126	CCTA	SVM	NA	Expert reader	No
Cho *et al.* (23)	2019	FFR classification	1,501	Invasive coronary angiography	XGBoost	NA	Invasive FFR	Yes
Liu *et al.* (24)	2019	Vulnerable plaque detection	2,300 (images)	OCT	CNN	NA	Expert reader	No
Gessert *et al.* (25)	2019	Coronary plaque segmentation	49	OCT	CNN	NA	Expert reader	No
Abdolmanafi *et al.* (26)	2019	Coronary artery wall pathology detection	45	OCT	CNN	NA	Expert reader	No
Liu *et al.* (27)	2019	Bifurcation lesion detection	308	Invasive coronary angiography	CNN	NA	Expert reader	No
Gharaibeh *et al.* (28)	2019	CAC quantification	34	IVUS	CNN	NA	Expert reader	No
Jun *et al.* (29)	2019	Thin cap fibroatheroma classification	100	IVUS	CNN	NA	OCT	No
Lee *et al.* (30)	2019	Coronary artery segmentation	4,980	Invasive coronary angiography	CNN	NA	Expert reader	No
Yang *et al.* (31)	2019	Coronary artery segmentation	2,042	Invasive coronary angiography	CNN	NA	Expert reader	Yes
Wang *et al.* (32)	2019	Media adventitia border detection	22	IVUS	MLP	P6 and P8 detectors	Expert reader	No
Johnson *et al.* (33)	2019	Clinical outcome prediction	6,892	CCTA	KNN	Conventional CT and clinical risk scores	Clinical outcomes	No
Kolossváry *et al.* (34)	2019	Coronary plaque classification	21	CCTA	Least angle regression + radiomics	Histogram assessment by expert reader	Histology (ex vivo)	No
Wang *et al.* (35)	2019	FFR prediction	63	CCTA	RNN	Conventional CCTA	Invasive FFR	No
Datong *et al.* (36)	2019	CAC detection	820 (images)	CCTA	CNN	NA	Expert reader	No
Oikonomou *et al.* (37)	2019	Clinical outcome prediction	5,487	CCTA	RF + radiomics	Conventional clinical risk scores	Clinical outcomes	Yes
Masuda *et al.* (38)	2019	Coronary plaque classification	78	CCTA	Extreme gradient boosting	Conventional CCTA	IVUS	No

Table 1 (*continued*)

Table 1 (*continued*)

First author	Year	Model output	Sample size	Imaging modality	Model	Index test	Reference test	External validation
Kigka *et al.* (39)	2019	Coronary plaque progression prediction	40	CCTA	RF	NA	Clinical outcomes	No
Zhang *et al.* (40)	2019	Coronary risk prediction	4,415	CCTA	Boosted ensemble algorithm	Conventional clinical risk scores	Clinical outcomes	No
Commandeur *et al.* (41)	2019	Epicardial adipose tissue quantification	850	CCTA	CNN	NA	Expert reader	No
Hong *et al.* (42)	2019	Coronary artery segmentation	156	CCTA	CNN	NA	Expert reader	No
Huo *et al.* (43)	2019	CAC detection	2,332	CCTA	CNN	NA	Expert reader	No
Wang *et al.* (44)	2020	MPVI prediction	9	IVUS	SVM and RF	GLMM	Follow-up MPVI	No
Lee *et al.* (45)	2020	FFR prediction	1,328	IVUS	AdaBoost	NA	Invasive FFR	No
Wu *et al.* (46)	2020	Coronary stenosis detection	63	Invasive coronary angiography	CNN	NA	Expert reader	No
Sampedro-Gómez *et al.* (47)	2020	Stent restenosis prediction	263	Invasive coronary angiography	ERT	Conventional clinical risk scores	Clinical outcomes	No
Miyoshi *et al.* (48)	2020	Coronary neointimal coverage classification, yellow colour classification, red thrombus detection	107	Invasive coronary angioscopy	GAN	SVM	Expert reader	Yes
Zhang *et al.* (49)	2020	Coronary stenosis classification	228	Invasive coronary angiography	HEAL	NA	Expert reader	No
Du *et al.* (50)	2021	Coronary artery segmentation, stenosis classification, total occlusion detection, calcification detection, thrombus detection, dissection detection	10,073	Invasive coronary angiography	CNN and GAN	NA	Expert reader	No
He *et al.* (51)	2020	Coronary plaque segmentation	24	OCT	CNN	NA	Expert reader	No
Yabushita *et al.* (52)	2021	Coronary artery segmentation	146	Invasive coronary angiography	CNN	NA	Expert reader	No
Hamaya *et al.* (53)	2020	Clustering epicardial functional stenosis with low CFR	364	Invasive coronary angiography	Unsupervised hierarchical clustering	K-mean clustering	Clinical outcomes	No
Lee *et al.* (54)	2019	Coronary plaque segmentation	55	OCT	CNN	A-line CNN detector	Expert reader	No
Min *et al.* (55)	2020	Thin cap fibroatheroma classification	602	OCT	CNN	NA	Expert reader	No
Commandeur *et al.* (56)	2020	Clinical outcome prediction	1,912	CCTA	Extreme gradient boosting	Conventional CT and clinical risk scores	Clinical outcomes	No
Muscogiuri *et al.* (57)	2020	CAD classification	288	CCTA	CNN	NA	Expert reader	No
Benz *et al.* (58)	2020	Coronary artery image reconstruction	43	CCTA	CNN	Adaptive statistical iterative reconstruction	Invasive coronary angiography	No
Wang *et al.* (59)	2020	CAC quantification	530	CCTA	CNN	NA	Expert reader	No
Al'Aref *et al.* (60)	2020	Coronary stenosis prediction from CACS	13,054	CCT	Boosted ensemble algorithm	NA	CCTA	No
Kawasaki *et al.* (61)	2020	FFR prediction	47	CCTA	RF	NA	Invasive FFR	No
Fischer *et al.* (62)	2020	CAC quantification	200	CCTA	RNN	NA	Expert reader	No
van Velzen *et al.* (63)	2020	CAC quantification	7,240	CCTA	CNN	NA	Expert reader	No
Zreik *et al.* (64)	2020	Coronary stenosis classification	187	CCTA	CNN + SVM	NA	Invasive FFR	No
Kumamaru *et al.* (65)	2020	FFR prediction	1,052	CCTA	CNN + GAN	Conventional CCTA	Invasive FFR	No
Candemir *et al.* (66)	2020	Coronary stenosis classification	493	CCTA	CNN	NA	Expert reader	Yes
Shu *et al.* (67)	2022	Clinical outcome prediction	154	CCTA	SVM + radiomics	NA	Expert reader	Yes
van den Oever *et al.* (68)	2020	CAC rule out	100	CCTA	CNN	NA	Expert reader	Yes
Han *et al.* (69)	2020	Coronary stenosis classification	150	CCTA	CNN	Expert reader	Invasive coronary angiography	No
Han *et al.* (70)	2020	Rapid plaque progression prediction	1,083	CCTA	Boosted ensemble algorithm	Conventional clinical risk scores	Clinical outcomes	No
Lin *et al.* (71)	2020	Pericoronary adipose tissue prognosis prediction	177	CCTA	Boosted ensemble algorithm + radiomics	Conventional CT and clinical risk scores	Clinical outcomes	No

Table 1 (*continued*)

Table 1 (*continued*)

First author	Year	Model output	Sample size	Imaging modality	Model	Index test	Reference test	External validation
Chen *et al.* (72)	2020	Coronary artery segmentation	124	CCTA	CNN	Expert reader	Invasive coronary angiography	No
Tesche *et al.* (73)	2021	Clinical outcome prediction	361	CCTA	Boosted ensemble algorithm	Conventional CT and clinical risk scores	Clinical outcomes	No
Al'Aref *et al.* (74)	2020	CL precursors detection	46	CCTA	Boosted ensemble algorithm	Traditional CCTA CL precursors	Invasive coronary angiography	Yes
Hong *et al.* (75)	2020	CCTA image noise reduction	82	CCTA	CNN	NA	Invasive coronary angiography	No
Podgorsak *et al.* (76)	2020	Coronary segmentation and FFR prediction	64	CCTA	CNN	Expert reader	Invasive FFR	No
Eberhard *et al.* (77)	2020	FFR prediction	56	CCTA	CNN	Invasive FFR	Clinical outcomes	No
Son *et al.* (78)	2020	CAC prediction	20,130	Retinal fundus imaging	CNN	NA	CCTA	No
Carson *et al.* (79)	2020	FFR prediction	25	CCTA	MLP and RNN	MPR	Invasive FFR	Yes
Gangl *et al.* (80)	2019	Coronary plaque segmentation	104 (images)	OCT	CNN	NA	Expert reader	No
Głowacki *et al.* (81)	2020	Coronary stenosis prediction from CACS	435	CCT	Extreme gradient boosting	NA	CCTA	No
Hoshino *et al.* (82)	2020	FAI clusters	220	CCTA	Unsupervised hierarchical clustering	Invasive FFR	Clinical outcomes	No
Kawaguchi *et al.* (83)	2018	FFR prediction	934	CCTA	CNN	NA	Invasive FFR	No

CCTA, coronary computed tomographic angiography; RF, random forest; SVM, support vector machine; IVUS, intra-vascular ultrasound; NA, not available; cIMT, carotid intima-media thickness; FFR, fractional flow reserve; MLP, multi-layer perceptron; CT, computed tomography; CAC, coronary artery calcification; CNN, convolutional neural network; OCT, optical coherence tomography; RNN, recurrent neural network; LV, left ventricle; CAD, coronary artery disease; cPSTA, cardiac phase space tomography analysis; CACS, coronary artery calcium score; KNN, k-nearest neighbours; MPVI, morphological plaque vulnerability index; GLMM, generalised linear mixed model; ERT, extremely randomised tree; GAN, generative adversarial network; HEAL, hierarchical attentive multi-view; CFR, coronary flow reserve; CL, culprit lesion; MPR, multi-variant polynomial regression; FAI, fat attenuation index.

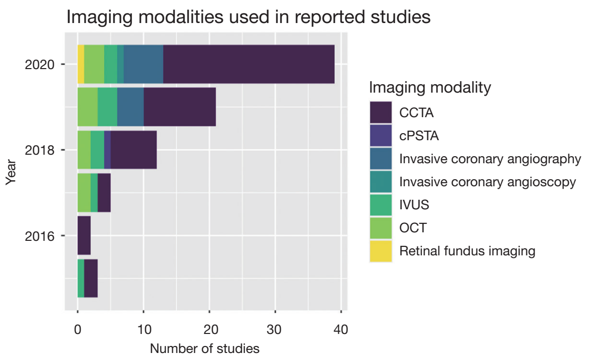

Figure 2 A stacked bar plot showing the number of studies for each imaging modality in the last 6 years. Some imaging modalities are very rare and not widely used, therefore they are not explained in the text but listed in the table and the bar plot, such as cPSTA and coronary angioscopy. Invasive coronary angioscopy is an old technique used for direct lumen visualisation using lenses and a light bulb, similar to endoscopic principles. One study of retinal fundus imaging was included as it used deep learning to predict coronary calcification compared to CCTA (78). CCTA, coronary computed tomographic angiography; cPSTA, cardiac phase space tomography analysis; IVUS, intra-vascular ultrasound; OCT, optic coherence tomography.

OCT and IVUS are performed during invasive coronary angiography to add more detailed imaging analysis of atherosclerotic lesions seen on Cine X-ray images.

The most commonly used deep learning technique was convolutional neural network (CNN) as shown in *Figure 3*, with more than half of the studies (52%) have used this approach as a single model or combined with other models. The use of multi-layer perceptron (MLP) was scarce with only 4 studies reported their results using MLP approach. There was a variety of models used with only a few studies in each category, including generative adversarial network (GAN), recurrent neural network (RNN), random forest (RF), gradient boost, support vector machine (SVM), to name a few.

Principle deep learning applications and meta-analysis

Coronary calcification

Several CCTA studies have focused on detection or quantification of coronary calcium given its prognostic importance in clinical outcomes. There have been successful applications of deep learning models using mainly CNNs to detect coronary artery calcification (CAC). Studies with

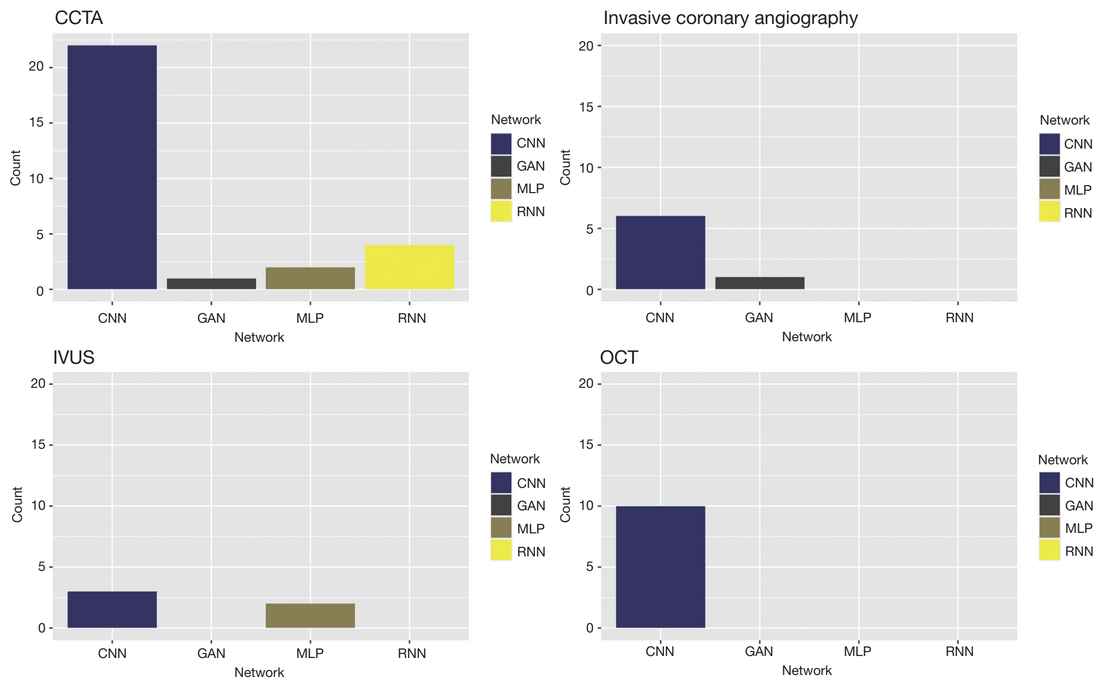

Figure 3 Bar plots showing the different neural networks models used based on the imaging modality used. CCTA, coronary computed tomography angiography; CNN, convolutional neural network; GAN, generative adversarial network; MLP, multi-layer perceptron; RNN, recurrent neural network; IVUS, intra-vascular ultrasound; OCT, optimal coherence tomography.

large sample sizes have been conducted and reported good or excellent model performance in detecting CAC. Huo *et al.* (43) used 2,332 of scan-rescan pairs as input to their CNN architecture called AID-Net, which is composed of 3D ResNet and 3D DenseNet layers. They reported high model performance with AUC as high as 0.93 in detecting CAC. van Velzen *et al.* (63) used a large sample of CCTA data from 7,240 participants, and with a CNN they quantified CAC and achieved a high model performance with 97% inter-class correlation with expert reader and 96% accuracy. All other studies had smaller sample sizes and reported similar level of performance for CAC detection and quantification using CNNs.

Fischer *et al.* (62) used RNN for CAC quantification, and their model achieved good performance with sensitivity of 92% and specificity of 89%. All these reports confirm that deep learning algorithms are capable of performing CAC detection or rule out, and quantification in a highly reliable way and with less time than an expert human reader.

Coronary artery stenosis

All of the four main imaging modalities (CCTA, OCT, IVUS, invasive coronary angiography) were used for deep learning applications to assess coronary stenosis in various ways: coronary plaque classification and segmentation, coronary stenosis classification and segmentation, culprit lesions predictors, vulnerable plaque precursors, thrombus, dissection and clinical outcome prediction.

Invasive coronary angiography studies used large numbers of patients for coronary artery segmentation. Du *et al.* (50) looked at 10,073 cases and trained a CNN and a GAN for better characterisation of coronary lesion location and description. Their model was able to perform coronary artery segmentation, stenosis classification, detection of total occlusion, calcification, thrombus and coronary dissection. They reported an AUC of 0.8 for coronary stenosis classification and F1 score of 0.82, and similar metrics for the other outputs were achieved, with a better performance in coronary segmentation with an AUC of 0.86. Similar performance was achieved from CCTA studies in coronary artery segmentation, Chen *et al.* (72) reported an AUC of 0.89 after using a CNN with 3D U-Net architecture on a sample size of 432 cases.

FFR

The earliest and most successful application of deep learning in atherosclerosis and coronary anatomy imaging was achieved in the assessment of FFR using CCTA, currently there are clinical applications available and it has gained a lot of attention in cardiovascular medicine and cardiothoracic surgery, due to the advantage of assessing coronary anatomy and ischaemic burden of coronary lesions both non-invasively.

The first application was in 2016 when Itu *et al.* (6) analysed 87 cases of CCTA and used a MLP architecture and some feature extraction techniques to calculate reliable FFR values, which was validated by invasive measurements. Also, this was compared to conventional CT-FFR based on computational fluid dynamics and showed to be more efficient. Their reported specificity was 84% and sensitivity 82% compared to invasive assessment. Many studies have been published since then to externally validate those findings and the algorithm has been tested for various applications beyond just the absolute FFR values, such as looking at clinical outcome and prognosis.

Following this successful application, several studies have used more developed deep learning techniques to predict CT-FFR using CNNs and RNNs, and they all reported high performance metrics after comparing with invasive FFR.

A meta-analysis has been performed on eight studies which reported FFR prediction and had sensitivity and specificity reported. *Figure 4* shows a coupled forest plot for sensitivity and specificity to assess heterogeneity by visual appreciation.

After calculating the DOR for all studies using MH method, the pooled value of DOR was estimated at 12.5. According to the literature this is considered as a positive finding as it is higher than 10 (84). *Figure 5* shows a forest plot of the natural logarithmic DOR (lnDOR) for all eight studies with the pooled value in the summary (MH).

Assessment of heterogeneity

Quantifying heterogeneity of the eight studies included in meta-analysis showed tau^2 =0.0011 with confidence interval (0.0000, 0.0166), this indicates no significant heterogeneity between studies.

I^2 was calculated at 22.6%, indicating that true effect size differences have affected less than quarter of the variation in our data. According to "rule of thumb" from the literature, heterogeneity based on this value is considered mild.

The predictive interval was ranging from (0.9006 to 1.1061), this means that based on the present evidence, it is possible that some future studies will likely find positive

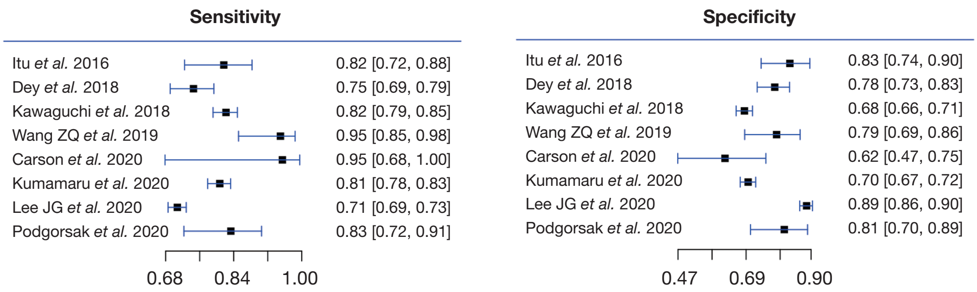

Figure 4 Forest plots showing summary of sensitivity and specificity across all eight studies in the meta-analysis.

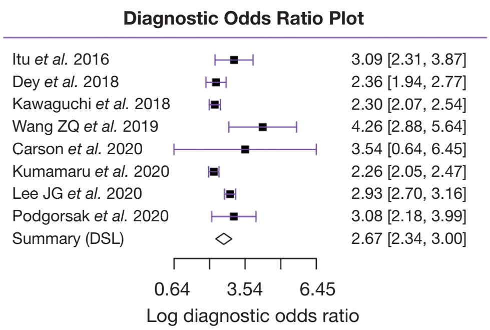

Figure 5 Forest plot showing summary of all DOR with the pooled summary, all reported in log values. DSL, DerSimonian-Laird meta-analysis; DOR, diagnostic odds ratio.

effect.

Finally, Q test has shown a P value above significance level (P=0.2496), which indicates that there is no significant heterogeneity.

Assessment of risk of bias

Overall, there was a low risk of study bias, a table of the included studies with their associated risk of bias is shown in Table S1. One of the main observations was that a significant number of studies (51 out of 81 studies) did not have a comparator conventional test to draw conclusion on the performance of the models compared to current practice. However, the majority of the studies reported reasonable information about their models and performance metrics.

Discussion

Deep learning techniques

The three main types of layers which compose artificial neural networks (ANNs) are: input layers taking the raw image data, hidden layers connected via weight vectors, and an output layer which takes the weighted sum, applies an output function and return a prediction.

The fully connected layers with MLP put significant limitation to the size of the model and the number of filters available to learn image features. CNNs overcome this challenge by using fully connected layers very sparsely, and with more focus on convolution layers using hundreds or thousands of filters, the values of which are learnt automatically during the training phase. The sequential nature of the layers of the CNN can be thought of in the following steps: the early layers detect edges from raw pixel data, these edges are then used to detect shapes in further layers, and these shapes are used to detect higher-level features in the later layers. An additional exciting property of neural networks is that they can be used with transfer learning where high-level feature extraction ability is kept by saving the majority of the network, and a new layer to fit with the purpose of the study is exchanged with the output layer (85).

GANs have been gaining more popularity recently in medical imaging, and we saw some novel applications which have been applied in CCTA and invasive coronary angiography, as shown in *Figure 3*. These networks were first introduced by Goodfellow *et al.* (86), and can be used to generate synthetic images that are perceptually similar to their ground truth, authentic originals. This can be achieved by training two neural networks, one is called the generator that accepts an input vector of randomly generated noise and produces an output “imitation” image that looks similar to an image from the training image domain, if not identical to an authentic image, and the other is called the discriminator which attempts to determine if a given image is an “authentic” or “fake”. By training both of these networks at the same time, one giving feedback to the other, we can learn to generate synthetic images. This model has been applied by Du *et al.* (50) successfully to unravel the complex features of coronary lesions seen in invasive coronary angiography by combining images from lesion location with images from lesion morphology to generate a high-level diagnostic information including identification of every coronary artery lesion and the coronary artery segment, in which it is located.

Finally, RNNs are type of neural networks which uses sequential data or time series data. They are distinguished by their memory as they take information from prior inputs to influence the current output. An RNN cell contains a closed-loop which allows the output of the current step to be influenced by the output of the previous step. Carson *et al.* (79) applied a RNN on CCTA to predict FFR based on the fact that coronary anatomy geometry has large variations including different vessel sizes, connectivity and the inclusion or exclusion of certain vessels. RNN has the advantage for providing the solution in the next vessel based on the solution of the previous vessel. This model had high performance compared to other non-invasive models and perfect sensitivity when compared with invasive FFR, however, it had very low specificity at 40% with high rate of FP FFR. This study had a small sample size of only 25 cases. Therefore, further testing and studies on RNN is required for further evaluation.

Summary of main results

This systematic review shows how extensive the work has been made in the last few years in the field of coronary anatomy and atherosclerosis imaging using machine learning and deep learning applications. Overall, all studies reported in this review (81 studies over 6 years) showed good performance of the models presented to achieve the target outputs for each individual study.

The most popular imaging modality which has been used extensively in deep learning application is CCTA, with a wide range of applications ranging from coronary anatomy segmentation, plaque classification, coronary calcium quantification, vulnerable plaque detection, noise reduction and image reconstruction, and clinical outcome prediction.

Invasive coronary angiography was a focus in deep learning in recent years, various applications looked at coronary segmentation, coronary stenosis classification, thrombus detection, total occlusion detection and dissection detection. Moreover, the intra-vascular coronary imaging modalities such as IVUS and OCT have been studied for the last few years for various applications, mainly linked to segmentation and characterisation of coronary artery lumen and plaque.

One of the major works, which shows how effective deep learning can be is the CT-FFR algorithm. Our meta-analysis of the 8 studies looking at deep learning applications to predict CT-FFR showed positive results of the pooled diagnostic performance and low level of heterogeneity. Furthermore, predictive interval tests showed that some future studies will likely find positive effect based on the present evidence. Although CT-FFR was performed initially by Itu *et al.* (6) using a MLP, it gained popularity after showing superior performance to computational fluid dynamics and was tested in several studies for external validation, which confirmed its utility in clinical applications. There is currently more focus on using more advanced deep learning techniques such as CNN, and this continues to show promising results.

The positive findings in all the presented studies could have an impact on clinical practice by introducing new developments to current state of the art imaging modalities, such as CCTA, IVUS, and OCT, and improve clinical workflow with faster diagnosis and more meaningful image analysis.

The quantification ability of deep learning and radiomics can unravel features and relationships in the medical images which are not easily detected by the human eye, however, this area still needs further studies to evaluate the clinical usage of such models, and the current review has set the scene for the potential, which computer vision could offer to achieve this goal.

Limitations

This review excluded studies which have been presented in computer vision competitions, which may underrepresent some of the effective techniques out in the industry, therefore, the list of the models listed here is not exclusive.

The presented studies in this review have reported a large variation of performance metrics, which made meta-analysis challenging and it is limited to only 8 studies.

Conclusions

Implications for practice

This review has shed light on an important rising field in cardiovascular imaging, deep learning and computer vision.

The tremendous advancement in coronary atherosclerosis imaging has already affected our practice with the use of non-invasive CT-FFR to make clinical decisions, and will soon change many other decisions we make in cardiovascular medicine. Although this is an exciting era of technology and precision medicine, clinical scrutiny and systematic review of the evidence is essential and should be periodic, in order to make the best possible decision for our patients.

Implications for research

There is a high demand for more research using novel deep learning applications on large datasets, in well-designed environments with robust study protocols, to achieve meaningful software applications, which are trustworthy and reliable to use on our patients.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://jmai.amegroups.com/article/view/10.21037/jmai-22-36/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 List of all studies with their corresponding risk of bias assessments

Study, year	Patient selection	Index test	Reference test	Index test results blinded	Reference test results blinded
Carson, 2020	?	–	+	–	?
Hoshino, 2020	+	+	+	?	?
Son, 2020	+	–	+	–	+
Eberhard, 2020	+	+	+	?	?
Wang, 2020	?	+	+	?	?
Hong, 2019	+	–	+	–	?
Podgorsak, 2020	+	+	+	?	?
Min, 2020	?	–	+	–	?
Wang, 2019	+	+	+	?	+
Lee, 2019	+	+	+	?	+
Hamaya, 2020	+	+	+	?	?
Yabushita, 2021	+	–	+	–	+
Hong, 2020	+	–	+	–	+
He, 2020	+	–	+	–	?
Gessert, 2019	+	–	+	–	?
Kang, 2015	+	+	+	–	+
Rodrigues, 2016	+	+	+	–	?
Wolterink, 2016	+	–	+	–	?
Al'Aref, 2020	+	+	+	+	+
Araki, 2016	+	–	+	–	?
Tesche, 2021	+	+	+	–	?
Chen, 2020	+	+	+	+	+
Du, 2021	+	–	+	–	?
Zhang, 2020	+	–	+	–	?
Lin, 2020	+	+	+	–	?
Xu, 2017	+	–	+	–	?
Yong, 2017	+	–	+	–	?
Kolluru, 2018	+	–	+	–	?
Huo, 2019	+	–	+	–	?
Han, 2020	+	+	+	?	?
Kawaguchi, 2018	+	–	+	–	?
Han, 2020	+	+	+	+	+
van den Oever, 2020	+	–	+	–	+
Shu, 2022	+	–	+	–	+
Candemir, 2020	+	–	+	–	?
Zhang, 2018	+	–	+	–	?
Miyoshi, 2020	+	+	+	?	+
Kumamaru, 2020	+	+	+	?	?
Zreik, 2020	+	–	+	–	?
Dey, 2018	+	+	+	+	+

Table S1 (*continued*)

https://dx.doi.org/10.21037/jmai-22-36

Table S1 (*continued*)

Study, year	Patient selection	Index test	Reference test	Index test results blinded	Reference test results blinded
Sampedro-Gómez, 2020	+	+	+	+	+
Šprem, 2018	+	–	+	–	?
van Velzen, 2020	+	–	+	–	?
Fischer, 2020	+	–	+	–	?
Zreik, 2019	+	–	+	–	?
Wu, 2020	+	–	+	–	?
Hae, 2018	+	–	+	–	?
Lessmann, 2018	+	–	+	–	?
Stuckey, 2018	+	–	+	–	+
Lee JG, 2020	+	–	+	–	?
van Rosendael, 2018	+	+	+	–	?
Commandeur, 2019	+	–	+	–	+
Kawasaki, 2020	+	–	+	–	+
Yang, 2019	+	–	+	–	?
Lee PC, 2019	+	–	+	–	?
Zhang, 2019	+	+	+	?	?
Al'Aref, 2020	+	–	+	–	?
Wang, 2020	+	–	+	–	?
Benz, 2020	+	+	+	+	+
Muscogiuri, 2020	+	–	+	–	?
Kigka, 2019	+	–	+	–	?
Jun, 2019	+	–	+	–	?
Gharaibeh, 2019	+	–	+	–	?
Głowacki, 2020	+	–	+	–	?
Su, 2017	+	–	+	–	?
Oh, 2018	+	–	?	–	-
Liu, 2019	+	–	+	–	?
Zreik, 2018	+	–	+	–	+
Abdolmanafi, 2019	+	–	+	–	?
Commandeur, 2020	+	+	+	+	+
Masuda, 2019	+	+	+	?	?
Gangl, 2019	+	–	+	–	?
Itu, 2016	+	+	+	?	?
Oikonomou, 2019	+	+	+	?	?
Datong, 2019	+	–	+	–	?
Liu, 2019	+	–	+	–	?
Wang, 2019	+	+	+	+	+
Kolossváry, 2019	+	+	+	+	+
Johnson, 2019	+	+	+	?	?
van Hamersvelt, 2019	+	+	+	?	?
Cho, 2019	+	–	+	–	?

+, no risk of bias; –, equivocal risk; ?, high risk of bias.

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