

Systematic Review

Machine Learning Application in Different Imaging Modalities for Detection of Obstructive Coronary Artery Disease and Outcome Prediction: A Systematic Review and Meta-Analysis

Peter McGranaghan ^{1,2,3,4,5,†} , Doreen Schoeppenthau ^{3,6,*,†} , Antonia Popp ^{1,2,7} , Anshul Saxena ⁴ , Sharat Kothakapu ⁴ , Muni Rubens ⁴, Gabriel Jiménez ⁸, Pablo Gordillo ⁹, Emir Veledar ¹⁰, Alaa Abd El Al ^{1,2,3}, Anja Hennemuth ^{2,3,7} , Volkmar Falk ^{1,2,3,11} and Alexander Meyer ^{1,2,3} 

¹ Deutsches Herzzentrum der Charité, Department of Cardiothoracic and Vascular Surgery, Augustenburger Platz 1, 13353 Berlin, Germany; peter.mcgranaghan@charite.de (P.M.); alexander.meyer@dhzc-charite.de (A.M.)

² Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Charitéplatz 1, 10117 Berlin, Germany

³ DZHK (German Center for Cardiovascular Research), Augustenburger Platz 1, 13353 Berlin, Germany

⁴ Baptist Health South Florida, Department of Advanced Analytics, Miami, FL 33136, USA

⁵ Semmelweis Doctoral College, Semmelweis University, 1088 Budapest, Hungary

⁶ Deutsches Herzzentrum der Charité, Department of Cardiology, Angiology and Intensive Care Medicine, 13353 Berlin, Germany

⁷ Deutsches Herzzentrum der Charité, Institute of Computer-assisted Cardiovascular Medicine (ICM), 13353 Berlin, Germany

⁸ School of Medicine, Ludwig Maximilian University of Munich, 80539 Munich, Germany

⁹ School of Medicine, University of Heidelberg, 69120 Heidelberg, Germany

¹⁰ School of Medicine, Emory University, Atlanta, GA 30322, USA

¹¹ Department of Health Science and Technology, ETH (Eidgenössische Technische Hochschule), 8092 Zürich, Switzerland

* Correspondence: doreen.schoeppenthau@dhzc-charite.de; Tel.: +49-30-4593-2452; Fax: +49-30-450-7-553-703

† These authors contributed equally to this work.



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Abstract

Background/Objectives: Invasive coronary angiography (ICA) is the gold standard for the diagnosis of coronary artery disease (CAD), with various non-invasive imaging modalities also available. Machine learning (ML) methods are increasingly applied to overcome the limitations of diagnostic imaging by improving accuracy and observer independent performance. **Methods:** This meta-analysis (PRISMA method) summarizes the evidence for ML-based analyses of coronary imaging data from ICA, coronary computed tomography angiography (CT), and nuclear stress perfusion imaging (SPECT) to predict clinical outcomes and performance for precise diagnosis. We searched for studies from Jan 2012–March 2023. Study-reported c index values and 95% confidence intervals were used. Subgroup analyses separated models by outcome. Combined effect sizes using a random-effects model, test for heterogeneity, and Egger’s test to assess publication bias were considered. **Results:** In total, 46 studies were included (total subjects = 192,561; events = 31,353), of which 27 had sufficient data. Imaging modalities used were CT ($n = 34$), ICA ($n = 7$) and SPECT ($n = 5$). The most frequent study outcome was detection of stenosis ($n = 11$). Classic deep neural networks ($n = 12$) and convolutional neural networks ($n = 7$) were the most used ML models. Studies aiming to diagnose CAD performed best (0.85; 95% CI: 82, 89); models aiming to predict clinical outcomes performed slightly lower (0.81; 95% CI: 78, 84). The combined c-index was 0.84 (95% CI: 0.81–0.86). Test of heterogeneity showed a high variation among studies ($I^2 = 97.2\%$). Egger’s test did not indicate publication bias ($p = 0.485$). **Conclusions:** The application of ML methods to diagnose CAD and

predict clinical outcomes appears promising, although there is lack of standardization across studies.

Keywords: machine learning; coronary imaging; coronary artery disease

1. Introduction

Coronary artery disease (CAD) is the primary cause of adult mortality in Europe and globally [1]. Invasive coronary angiography (ICA) remains the gold standard for diagnosing CAD [2]. In ICA, the two-dimensional visual assessment of lumen diameters and stenosis by the physicians is poorly reproducible, highly variable, and prone to bias [3–5]. Therefore, offline quantitative coronary angiography was developed, which is often used in clinical trials but rarely in clinical practice.

ICA might not capture the complexity of certain lesions in specific segments and does not include information about plaque formation, but additional intraluminal imaging is costly and not widely available [6]. Multiple non-invasive imaging modalities are available for assessment in patients with suspected or confirmed chronic coronary syndromes. The latter play a critical role for the diagnosis of chronic CAD and evaluation of a patient's response to therapy. According to the European Association of Cardiovascular Imaging, coronary computed tomography angiography (CT), and nuclear stress perfusion imaging (SPECT) are the most often used radiologic modalities in Europe [7]. Despite the high-resolution imaging provided by coronary CT, the specificity is reduced by coronary calcium and elevated heart rates and irregular rhythms can make it challenging to assess certain coronary artery segments because of motion [8]. SPECT is limited due to patient motion and spatial misalignment as well as photon attenuation [9]. Selecting the appropriate imaging technique based on pre-test probability can enhance imaging-based quantification, advocating CT for patients with intermediate probability and invasive methods for those with acute or high-probability cases [10].

Machine learning (ML) approaches have the potential to significantly improve accuracy and provide consistent performance in this area of cardiovascular imaging. ML algorithms have become the favored method for analyzing medical imaging datasets, allowing for the construction of models that detect correlations between various data features. These correlations are identified using 'seen' input data and then applied to new, 'unseen' data to make predictions [11]. In cardiovascular medicine, physicians are challenged with data rich technologies (imaging, biometrics, etc.), requiring more sophisticated interpretation while demanding more efficiency [12].

The objective of this systematic review and meta-analysis is to assess the performance of ML-based analysis across various coronary imaging modalities for the detection of lesions and prediction of clinical outcomes in coronary artery disease (CAD). In this review, 'clinical outcomes' refer to diagnostic outcomes (presence or severity of coronary artery disease) and prognostic outcomes (including myocardial infarction, all-cause mortality, and other major adverse cardiac events). Model performance was operationally defined as the reported c-statistic or area under the curve (AUC) as a metric for predictive value. Through summarizing ML methodologies and evaluating their predictive value, this study aims to provide insights into the potential of ML in enhancing CAD diagnosis and management.

2. Materials and Methods

2.1. Systematic Review Methods

This systematic review was performed in accordance with the guidelines for Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [13]. PubMed, Google Scholar, and Web of Science databases were searched using key words to identify relevant articles. The review protocol is not registered in database of prospectively registered systematic reviews. Studies over the last 10 years (January 2013–March 2023) were included in this study. Our initial search filter used the term ‘coronary angiography’ along with its synonyms, connected by the Boolean operator OR. The second filter applied the terms ‘machine learning’ and its synonyms, also linked with the operator OR. The final filter included the terms ‘diagnosis’ OR ‘prognosis’ and their synonyms, connected by OR. These filtered searches were then combined using the Boolean operator AND. Keywords that did not yield relevant results for this study were subsequently filtered out. For instance, some studies that focused on the automatic quantitative parameter calculations (CAC, FFR), image processing and segmentation were excluded. Papers satisfying all inclusion and exclusion criteria were further analyzed and relevant data was extracted. The literature search was validated by two independent reviewers.

The inclusion criteria for the systematic review were studies applying ML methods to radiological coronary imaging for the purpose of diagnosing CAD or predicting clinical outcomes. Specifically:

- Human studies using coronary images
- Machine learning methods
- Discrimination statistics of prediction models reported
- Peer-reviewed studies published from January 2013–March 2023.

The exclusion criteria were studies using physiological simulations (e.g., CT-FFR not yet in clinical practice), non-radiological imaging modalities (e.g., echocardiography, IVUS/OCT, cardiac MRI), animal studies, case reports, or non-original research (e.g., editorials, reviews). Specifically:

- Image processing studies
- Quantitative parameter calculations
- Absence of clinical outcomes

2.2. Meta-Analysis Methods

Inputs in the meta-analysis were the study-reported c-index or the area under curve and 95% confidence interval (CI). Subgroup analyses were separated by models according to their outcome group based on the type of prediction study: diagnosis or prognosis. Diagnosis was defined as the process of identification or characterization of specific pathological traits (lesion specific ischemia, functionally significant stenosis, lesion precursors, atherosclerotic plaque, or plaque progression). Prognosis was defined as the prediction of short- or long-term clinical outcomes due to CAD (cardiovascular death, myocardial infarction (MI), major adverse cardiovascular events (MACE), need for revascularization). Combined effect sizes using a random-effects model, test for heterogeneity, and Egger’s test to assess publication bias were used.

Only studies which reported discrimination statistics, and 95% CI were included. Effect sizes (AUC, c-statistic), confidence intervals, and number of observations from the best performing model from each study were included in the analysis. For example, if studies used a discovery and validation/replication approach or an ensemble approach for building multiple ML models, the model with the largest AUC/c-statistic was considered, meaning only one model was selected from each study to be included in the meta-analysis.

Our main method was the random-effects model, as it accounts for both within-study and between-study variance. Heterogeneity of effect sizes was measured using the Cochran Q test and I^2 statistic, with a threshold of 30% indicating at least moderate heterogeneity. Publication bias was evaluated by visually inspecting funnel plots. Egger's regression test (with $p < 0.05$ suggesting bias) was used to assess funnel plot asymmetry and the skewness of standard error distribution around the effect estimates. A significance level of $p < 0.05$ was applied to denote significant funnel plot asymmetry. Meta-analysis was performed using the metan package in Stata 14.2 (StataCorp), with a two-tailed $p < 0.05$ considered statistically significant. The assessment of publication bias and heterogeneity was carried out using Meta Essentials [14].

The discussion of algorithm selection, technical explanation of algorithm function, and explanation of supporting mathematics are not described because they are beyond the scope of this work.

3. Results

The central illustration summarizes the systematic review and meta-analysis study design and results.

3.1. Systematic Review Results

Using a combination of search filters with 10 different keywords, separated by the Boolean operators 'OR' and 'AND' (see Supplemental Table S1), we retrieved 1379 articles from PubMed, 4540 from Google Scholar, and 558 from Web of Science. From these, 2397 abstracts were reviewed for relevance based on their titles and subsequently excluded. After the final exclusion process, 46 publications were selected for further analysis, encompassing 192,561 subjects and 31,353 clinical outcomes. Figure 1 summarizes the results of the literature search and study selection.

The majority of studies ($n = 34$) used CT for coronary angiography while 7 studies used ICA and 5 used SPECT. The most studied outcome group was diagnosis ($n = 32$) vessel stenosis ($n = 19$), ischemia producing lesions ($n = 8$) coronary plaques ($n = 4$), peripheral artery disease ($n = 1$) followed by prediction of adverse events ($n = 14$) composite outcomes ($n = 5$), mortality ($n = 4$), necessity for revascularization ($n = 2$), major adverse cardiovascular events (MACE) ($n = 2$), and myocardial infarction ($n = 1$). The most common ML models used for predicting outcomes were, DNN ($n = 12$), CNN ($n = 7$) and XGboost ($n = 7$). There were studies which used customized DNN architectures such as hierarchical convolutional long short-term memory (ConvLSTM) network [15], deep sparse overcomplete autoencoder model [16], a fully connected network model [17], while almost half of the DNN studies used commercially available or pre-configured tools [18–22]. The median of sample sizes of the extracted models was 527 (interquartile range [IQR], 166–1755) and 10 studies externally validated their model. There were 16 studies that used an unsupervised approach while the rest used only a supervised ML approach. There were 30 studies which used image analysis algorithms for feature extraction prior to building the prediction model while the rest used structured angiogram data for their prediction model. Most studies ($n = 32$) used only image variables for their prediction models; all others integrated clinical, demographic, and laboratory variables in the model. Table 1 summarizes the general study characteristics.

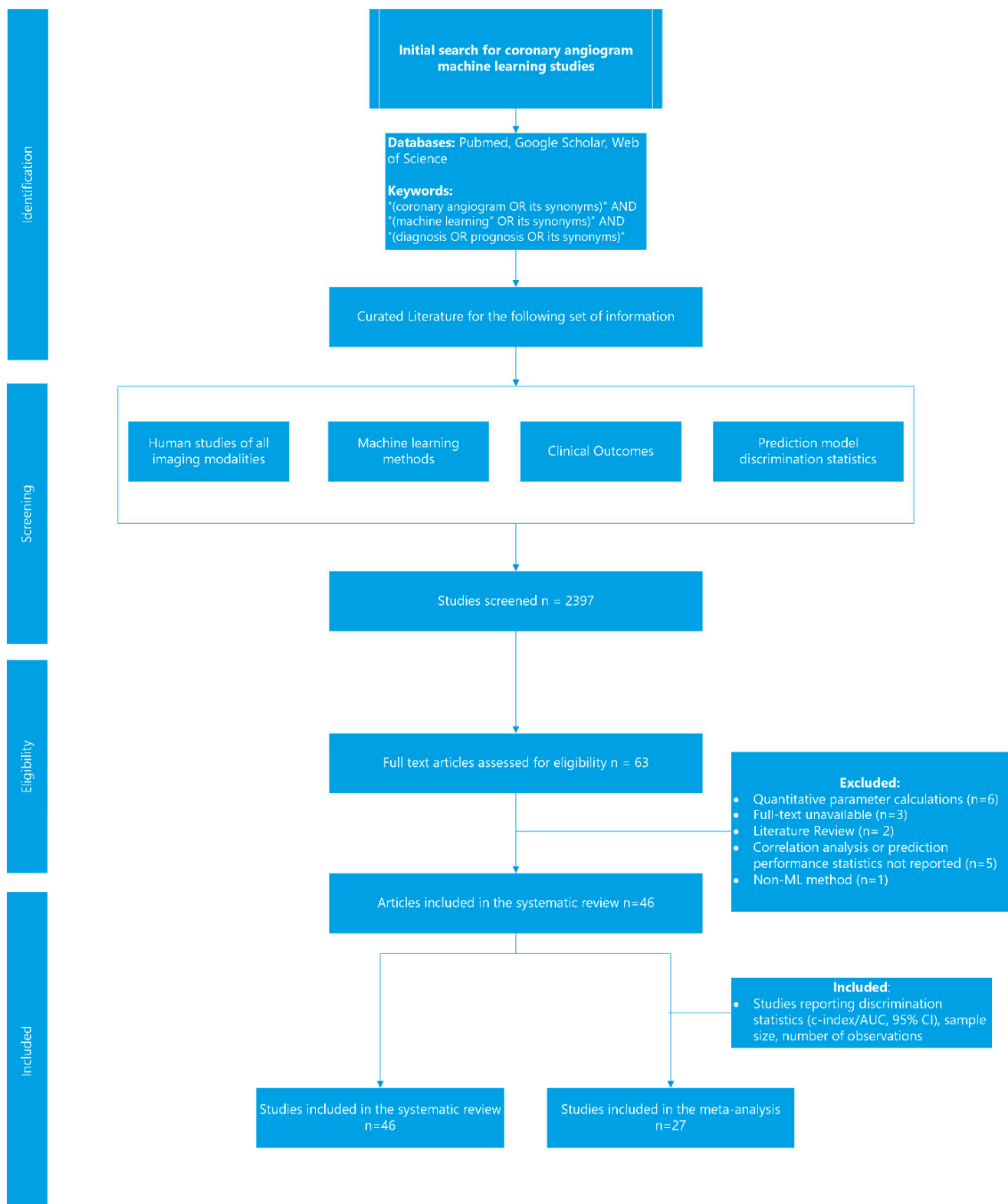


Figure 1. Flowchart of the systematic review of coronary angiogram machine learning studies.

Table 1. Summary of studies included in the systematic review.

Study	Effect Size	Outcome	Sample Size	Events	Population	Model	Image Modality
Lin 2022 [15]	0.7 (0.68–0.73)	Prediction of MI	912	41	Patients with suspected CAD	DNN	CT
Freiman 2019 [16]	0.94	Detection of severe stenosis	90		Patients with suspected CAD	DNN	CT
Tesche 2018 [17]	0.91 (0.84–0.97)	Detection of lesion specific ischemia	104	34	Patients with CAD	DNN	CT
Chen 2020 [18]	0.78 (0.63–0.93)	Diagnosis of obstructive CAD	124	108	Patients with suspected CAD	DNN	CT
Li 2019 [19]	0.85	Detection of functionally significant stenosis	157	99	Patients with stable angina	DNN	CT
Duguay 2017 [20]	0.78 (0.63–0.89)	Prediction of MACE	48	14	Patients with suspected ACS	DNN	CT
Griffin 2023 [21]	0.92 (0.89–0.95)	Detection of severe stenosis	303	207	Patients with suspected CAD	DNN	CT
Xu 2021 [22]	0.81 (0.79–0.83)	Detection of severe stenosis	527	440	Patients with suspected CAD	DNN	CT
Arsanjani 2013 [23]	0.94 (0.93–0.95)	Diagnosis of obstructive CAD	1181	416	Patients with suspected CAD	LogitBoost	ICA
Betancur, Slomka 2018 [24]	0.77 (0.75–0.79)	Diagnosis of obstructive CAD	1638	1018	Patients without CAD	CNN	SPECT
Kang 2015 [25]	0.94 (± 0.03)	Detection of obstructive and nonobstructive lesions	42	21	Patients with and without CAD	SVM	SPECT
Dey 2018 [26]	0.84 (0.79–0.88)	Detection of lesion specific ischemia	1687	80	Patients with suspected CAD	LogitBoost	CT
Johnson 2019 [27]	0.85 (0.84–0.85)	Prediction of CVD Death	6892	70	Patients with suspected CAD	KNN	CT
van Rosendaal 2018 [28]	0.771	Prediction of MI and death	8844	609	Patients without CAD	XGboost	CT
Motwani 2017 [29]	0.79 (0.77–0.81)	Prediction of 5-year all-cause mortality	10,030	745	Patients with suspected CAD	LogitBoost	CT
Al’Aref, Min 2020 [30]	0.77 (0.76–0.79)	Detection of culprit lesion precursors	468	124	Patients with ACS	XGboost	CT
Al’Aref, Shaw 2020 [31]	0.88 (0.87–0.90)	Diagnosis of obstructive CAD	13,064	2380	Patients with suspected or previously established CAD	XGboost	CT
AlOthman 2022 [32]	0.93	Detection of stenosis	200	100	Patients with suspected CAD	CNN	CT
Baskaran 2020 [33]	0.96 (0.93–0.98)	Prediction of necessity for revascularization	1503	159	Patients with suspected CAD	XGboost	CT
Betancur, Awai 2018 [34]	0.8 (0.77–0.83)	Prediction of MACE	1638	1018	Patients without CAD	CNN	SPECT
Cho 2019 [35]	0.87 (± 0.16)	Detection of lesion specific ischemia	1501	700	Patients with CAD	XGboost	ICA
Commandeur 2020 [36]	0.82 (0.71–0.93)	Prediction of MI and cardiac death	1912	76	Patients with suspected CAD	CNN	CT
Cong 2023 [37]	0.86	Characterization of stenosis	194	194	Patients with suspected CAD	DNN	CT
Du 2021 [38]	0.86	Characterization of vessel lesion	20,612	12,184	Patients with and without CAD	cGAN	ICA
Hae 2018 [39]	0.89 (0.83–0.95)	Detection of lesion specific ischemia	200	25	Patients with suspected CAD	Light GBM	CT
Han 2018 [40]	0.75 (0.69–0.81)	Detection of lesion specific ischemia	252	129	Patients with suspected CAD	GBM	CT

Table 1. Cont.

Study	Effect Size	Outcome	Sample Size	Events	Population	Model	Image Modality
Han 2020 [41]	0.83 (0.78–0.89)	Detection of rapid coronary plaque progression	1083	224	Patients with suspected CAD	LogitBoost	CT
Haro Alonso 2019 [42]	0.83	Prediction of cardiac death	8321	551	Patients with suspected or previously established CAD	SVM	CT
Hu 2020 [43]	0.81 (0.79–0.83)	Prediction of necessity for revascularization	1980	958	Patients with suspected CAD	LogitBoost	SPECT
Hu 2021 [44]	0.8 (0.79–0.81)	Prediction of MACE	20,414	3541	Patients with suspected CAD	XGboost	SPECT
Kwan 2020 [45]	0.78 (0.75–0.81)	Prediction of Revascularization	352	208	Patients with suspected CAD	LogitBoost	CT
Li 2022 [46]	0.737	Detection of stenosis	443	154	Patients with suspected CAD	DNN	CT
Mahendiran 2022 [47]	0.81	Prediction of future culprit lesion	746	203	Patients with MI	DNN	ICA
Masuda 2018 [48]	0.92	Characterization of coronary plaque	78	78	Patients with CAD	XGboost	CT
Moon 2021 [49]	0.971	Detection of functionally significant stenosis	452	221	Patients with suspected CAD	CNN	ICA
Nakanishi 2021 [50]	0.85 (0.83–0.86)	Prediction of CVD Death	66,636	1495	Patients with suspected CAD	LogitBoost	CT
Ross 2016 [51]	0.87 (0.83–0.98)	Diagnosis of PAD	1755	183	Patients with suspected CAD	RF	ICA
Sheth 2019 [52]	0.88 (0.83–0.92)	Detection of large vessel occlusion	297	124	Patients with and without TIA or AIS	CNN	CT
Shu 2021 [53]	82.7% (Accuracy)	Diagnosis of Myocardial Ischemia	75	50	Patients with suspected CAD	CNN	ICA
van Hamersvelt 2019 [54]	0.76 (± 0.02)	Detection of functionally significant stenosis	136	81	Patients with suspected CAD	SVM	CT
Wang 2019 [55]	0.93 (± 0.01)	Detection of lesion specific ischemia	63	35	Patients with CAD	RNN	CT
Wei 2014 [56]	0.87 (0.81–0.92)	Detection of noncalcified plaques	120	111	Patients with CAD	Linear Discriminant Classifier	CT
Xiong 2015 [57]	0.73	Detection of obstructive coronary artery stenoses	140	56	Patients with and without CAD	AdaBoost	CT
Yang 2021 [58]	0.706	Prediction of cardiac death, MI, or revascularization	643	177	Patients with suspected CAD	RF	CT
Zhao 2019 [59]	92.6 (Precision)	Detection and classification of atherosclerotic plaque	14,628	1786	Patients with suspected CAD	SVM	CT
Zreik 2018 [60]	0.74 (± 0.02)	Detection of functionally significant stenosis	166	126	Patients with CAD	SVM	CT

3.2. Meta-Analysis Results

The meta-analysis included 27 studies (135,183 subjects, 13,963 events). The combined effect for all studies was 0.84 (0.81–0.86), and the heterogeneity was high ($I^2 = 97.2\%$, $p < 0.001$) with each subgroup showing similar heterogeneity. Most of the studies ($n = 19$) reported a c-index greater than 0.80, and no study reported a c-index less than 0.70. The subgroup with the highest effect size was the diagnosis group (0.85, 0.82–0.89), with the

prognosis group slightly lower at 0.81 (0.78–0.84). Publication bias was not detected, as the regression test did not show funnel plot asymmetry ($p = 0.485$). The funnel plot for publication bias is displayed in Supplemental Figure S1. Figure 2 presents the forest plot of effect sizes and 95% confidence intervals for the included studies, categorized by outcome group and subgroup.

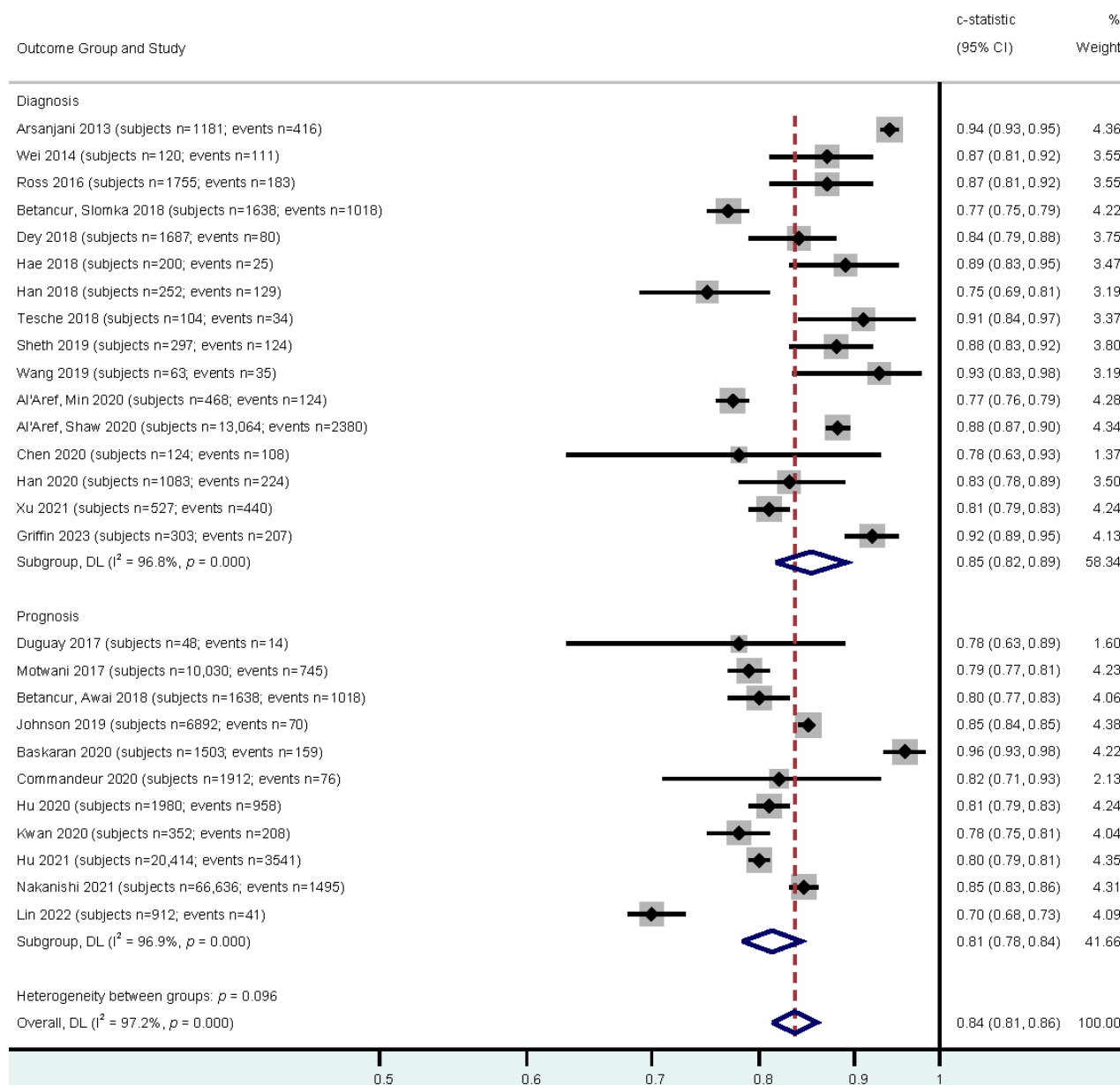


Figure 2. Forest plot of effect sizes of coronary angiogram machine learning studies and combined effect sizes with subgroup analysis of outcome group. References: [15,17,18,20–24,26,27,29–31,33,34,36,39–41,43–45,50–52,55,56].

4. Discussion

This review and meta-analysis summarize the available evidence of applications using ML to diagnose CAD and predict clinical outcomes based on radiological coronary imaging analysis.

The recent emergence of ML applied to coronary imaging to detect disease and lesions and to predict clinical outcomes shows promise [61–64]. Previous reviews covered a broad range of cardiac diseases and outcomes whereas our review focused exclusively

on ML applications used for clinical outcome prediction and the detection of coronary lesions (culprit lesion precursors, lesion specific ischemia, stenosis, rapid coronary plaque progression, obstructive and nonobstructive lesions, non-calcified plaques, characterization of vessel lesions or coronary plaques).

Numerous ML algorithms have been created to extract clinically significant information from cardiovascular images. Initially, these algorithms necessitated manual adjustment to convert input images into the desired output, whereas contemporary algorithms employ greater level of automation [65].

In addition to ML studies, traditional statistical models have also contributed to the understanding of CAD diagnosis and prognosis. However, traditional statistical models are not capable of performing actual image analysis, as this task typically requires the advanced capabilities of ML algorithms.

Unlike ML-based approaches, which can leverage advanced algorithms to analyze intricate imaging features and identify nuanced patterns associated with CAD, traditional statistical models rely on predefined relationships between variables and may struggle to capture the full complexity of imaging data.

Despite these limitations, traditional statistical models and ML-based approaches share similarities in their approach to analyzing clinical and imaging data for CAD diagnosis and prognosis. Both methods aim to identify predictive factors and develop models capable of accurately predicting disease outcomes. However, ML-based approaches offer distinct advantages in their ability to handle complex imaging data and extract subtle patterns, thus enhancing the accuracy and reliability of CAD diagnosis and prognosis.

In severe three-vessel CAD, the SYNTAX score calculation for anatomical complexity based on ICA was implemented into clinical practice in 2009 but is, therefore, dependent on thorough visual assessment of lesions by experienced physicians. It is supposed to help to identify the optimal myocardial revascularization strategy while a higher SYNTAX score suggests more complex disease, potentially favoring coronary artery bypass grafting (CABG), whereas lower scores might lean towards percutaneous coronary intervention (PCI) [66]. The score was adapted over time including clinical comorbidities and later, functional parameters derived by CT scans using fractional flow reserve (FFR)-imaging [67]. ML might further improve the performance of decision-making algorithms in this complex subgroup of patients. A significant milestone could be the application of ML and artificial intelligence to provide the practitioner with a non-invasive, automatic, objective, and reproducible analysis of the anatomic and functional SYNTAX score derived from FFR CT scans [67].

This review did not include studies with physiological simulation techniques that model coronary flow from coronary CT angiography or FFR measurements in ICA since this is not part of clinical practice so far. However, the hemodynamic significance of coronary stenosis in CAD is crucial. In CT Fractional Flow Reserve (FFR) measurements in moderate to severe anatomically identified stenosis can guide the need for interventions like angioplasty [68].

This emphasizes the need for a more detailed, personalized evaluation of CAD, combining insights from multiple disciplines to enhance diagnosis and treatment [69].

The specific clinical outcomes of interest for this study are discussed below. The grouping of outcomes (diagnosis, and prognosis) was an attempt to homogenize (reduce heterogeneity) of the overall meta-analysis and assess the focus/goals of earlier studies.

4.1. Diagnostic Studies

Our review shows that most of the existing coronary imaging ML studies focused on diagnosing CAD or detecting coronary lesions. Importantly, ML-studies aiming to diagnose CAD perform better than studies aiming to predict cardiovascular prognosis.

ML models have been most frequently applied in imaging. Techniques like segmenting images or deriving quantitative parameters are used.

Deep learning also has the potential to improve interpretation of functional coronary imaging, like nuclear stress perfusion imaging (SPECT). In two larger studies with 1181 and 2619 patients [23,24] LogitBoost ML for automated analysis of the perfusion deficits was found to be superior to standard visual interpretation by physicians in those studies.

Detection and quantification of lesions in coronary CT imaging is limited due to spatial resolution, heart rate and subsequent artery motion and additionally relatively small plaque size, leading to a substantial inter-observer variability [68,69]. Automated lesion detection in coronary CT requires accurate extraction of coronary arteries. Simple computer algorithms often show low specificity with large false positive detections while ML in coronary CT seems to have a good sensitivity and specificity [70]. Kang et al [25] determined the degree of coronary stenosis with the help of lumen segmentation in small volume patches. The study group detected obstructive (>50% narrowing) and non-obstructive lesions by combining geometrical and plaque features in a support vector machine- based learning algorithm very well [25].

A study by Freiman et al., found that deep sparse autoencoders could detect stenosis in coronary CT, with at least intermediate severity (>40% narrowing) [16].

It is usually necessary to locally measure the diameter of the vessel and estimate what a healthy lumen diameter would serve as a reference. The luminal diameter can be estimated to a large extent with automated extraction and estimation techniques which assume that the coronary arteries follow a circular profile at each point on the centerline [65,71]. A lumen segmentation process can also be initiated using the centerline estimates that are automatically extracted. For example, Huang et al. applied a 3D CNN to obtain compromised lumen segmentation masks based on centerlines of the vessels [72]. Despite the variability in methodologies and the diversity of studies included in this analysis, diagnostic studies demonstrate a significant impact, likely attributed to tailored approaches and more consistent definitions of outcomes.

4.2. Prognostic Studies

The fact that predicting outcomes with ML is less precise (e.g., smaller subgroup c-statistic) than CAD detection as shown in our meta-analysis implies that information about flow characteristics, plaque formation as well as clinical parameters (biomarkers, ECG parameters, echo parameters, texts from imaging reports, clinical notes, etc.) need to be integrated into complex ML models to provide rapid and precise disease classification and make better predictions on outcomes.

Plaque morphology and composition largely determine the risk of future cardiovascular events, surpassing the importance of individual stenosis severity [30]. Indeed, a significant portion of future myocardial infarctions (MIs) result from occlusion in arteries with minor stenosis [31], underscoring the critical importance of vulnerable plaque identification. In this context, these features should be viewed as increasingly vital in the evaluation of ML CT based prognostic features, given their pivotal role in improving predictive models [32].

Many studies have demonstrated that an objective ranking of ALL available clinical and imaging measures using ML is the most effective approach for predicting risk. For example, in a multicenter study, contrast densities differed significantly from plaque

metrics and quantitative stenosis measured with CTA for lesion-specific ischemia [26]. The ML model was able to predict ischemia related events with greater accuracy and precision, compared to traditional clinical and statistical methods. Similarly, Johnson et al. demonstrated that an ML model that includes per-segment coronary artery characteristics surpasses traditional scores in predicting cardiac events [27]. Van Rosendael et al. created a model for predicting all-cause mortality or myocardial infarction based solely on CTA scan features, which exceeded the performance of existing CTA-based risk scores [28]. Motwani et al. designed a model to predict five-year all-cause mortality using stenosis scores and plaque characteristics, outperforming current scores and clinical features [29].

ML techniques hold significant promise for the rapid and accurate prediction of clinical outcomes by integrating multimodal data sources, such as imaging modalities and clinical information extracted from electronic health records. This could alleviate clinicians from time-consuming tasks and transform diagnostic procedures, thereby potentially improving patient outcomes and reducing healthcare costs.

Given the growing relevance of ML in cardiovascular diagnostics, it is also essential to consider its role in the context of acute coronary syndrome (ACS), a clinical entity with high morbidity and diagnostic complexity. As highlighted by Mariani et al [73], Artificial intelligence (AI) based algorithms integrating clinical, electrocardiographic, and laboratory data have demonstrated superior performance compared to conventional diagnostic tools in detecting both STEMI and NSTEMI, as well as in predicting major adverse cardiovascular events and mortality. The future of AI in ACS management lies in the integration of multimodal data streams—including ECG, imaging, biomarkers, and clinical variables—to enable real-time, individualized risk stratification.

Nonetheless, as emphasized by Sharmeer et al [74], significant barriers to routine clinical adoption remain, including the need for external validation, standardized protocols, and seamless integration into clinical workflows. Addressing these challenges will be critical to translate the promise of AI into practical tools for acute cardiac care.

4.3. Study Limitations

The main limitations include variations in methodologies and study populations, incomplete dataset availability, and the absence of a standardized protocol for image analysis. Published results on ML-based CAD clinical outcome prediction show significant differences in datasets analyzed, sample sizes, features, data collection locations, performance metrics, and applied ML techniques. Consequently, these fundamental differences prevent the generalization of findings across the literature. Inclusion of only the best-performing models from each study may lead to overestimation of true model performance due to potential selective reporting. Another limitation is that calibration metrics—essential for assessing whether models systematically over- or under-predict risk—were not consistently reported across studies. As a result, our analysis focused primarily on discrimination metrics such as the c-index. Future studies should routinely report calibration performance to ensure clinical applicability of ML models.

The diagnosis and prognosis subgroups were created in an attempt to reduce heterogeneity of the meta-analysis; however, there could be overlap between subgroup definitions or studies could have analyzed multiple outcomes. Even with this grouping, the subgroups still showed high heterogeneity, limiting the meaningfulness of the combined effect sizes. This remaining heterogeneity underscores the complexity of variability drivers in ML studies for CAD.

An important limitation is that many studies did not validate the applied algorithms in separate cohorts. This lack of external validation can raise concerns about the algorithms' generalizability and effectiveness across different populations or clinical settings. A formal

study quality assessment (e.g., using QUADAS-2 or PROBAST) was not performed, which may limit the interpretability of pooled results.

Furthermore, the inclusion of studies from 2012 to 2023 inevitably introduced technological heterogeneity, as ML methods have evolved considerably during this period. This underscores the need for future benchmarking studies using standardized datasets and contemporary ML architectures.

Another limitation is that not all modalities for cardiovascular imaging were included in the analysis (e.g., cardiac MRI, Stress-Echo, resting longitudinal strain, ICA with IVUS/OCT) as we focused on radiological imaging of the coronary arteries, which is more ubiquitously available and typically follows standardized acquisition protocols.

The limited accessibility and non-uniform implementation of these alternative imaging techniques pose challenges for assembling large, consistent datasets suitable for ML development and validation. In line with this, our review shows a predominance of CT-based studies, likely reflecting its broader clinical adoption, high spatial resolution, and suitability for automated analysis workflows. However, this overrepresentation may introduce modality-specific bias and restrict the generalizability of our findings to other imaging platforms, emphasizing the need for further ML research leveraging underrepresented modalities.

5. Conclusions

This review provides evidence that machine learning approaches have the potential to provide additional diagnostic and prognostic value. Given the high heterogeneity, the pooled estimates should be interpreted with caution, and results should be considered exploratory rather than definitive. Nevertheless, this review highlights the potential for the implementation of ML in clinical settings which could significantly improve physicians' capacity to diagnose and promptly treat these conditions, thus in turn improving patient outcomes. Future studies should prioritize external validation in independent cohorts to ensure generalizability and clinical applicability of ML models. This could lead to better penetration of ML systems in real world settings to facilitate the generalized well-being of all patients affected by CAD.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/hearts6030021/s1>, Table S1. Literature search results for coronary imaging machine learning studies. Figure S1: Funnel plot for publication bias of the meta-analysis for coronary angiogram machine learning studies.

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