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Systematic Review/Meta-analysis

Artificial Intelligence for Diagnosis of Acute Coronary Syndromes: A Meta-analysis of Machine Learning Approaches

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See editorial by Miller, pages 470–473 of this issue.

ABSTRACT

Background: Machine learning (ML) encompasses a wide variety of methods by which artificial intelligence learns to perform tasks when exposed to data. Although detection of myocardial infarction has been facilitated with introduction of troponins, the diagnosis of acute coronary syndromes (ACS) without myocardial damage (without elevation of serum troponin) remains subjective, and its accuracy remains highly dependent on clinical skills of the health care professionals. Application of a ML algorithm may expedite management of ACS for either early discharge or early initiation of ACS management. We aim to summarize the published studies of ML for diagnosis of ACS.

Methods: We searched electronic databases, including PubMed, Embase, and Web of Science from inception up to January 13, 2019, for studies that evaluated ML algorithms for the diagnosis of ACS in patients presenting with chest pain. We then used random-effects bivariate meta-analysis models to summarize the studies.

Results: We retained 9 studies that evaluated ML in a total of 6292 patients. The prevalence of ACS in the evaluated cohorts ranged from relatively rare (7%) to common (57%). The pooled sensitivity and specificity were 0.95 and 0.90, respectively. The positive predictive

RÉSUMÉ

Contexte : L'apprentissage automatique englobe une grande variété de méthodes par lesquelles une intelligence artificielle apprend à exécuter certaines tâches à partir des données qu'on lui fournit. Bien que l'analyse des troponines facilite aujourd'hui la détection de l'infarctus du myocarde, le diagnostic des syndromes coronariens aigus (SCA) sans lésion myocardique (sans élévation des troponines sériques) demeure subjectif, et son exactitude dépend fortement des compétences cliniques des professionnels de la santé. L'application d'un algorithme d'apprentissage automatique peut accélérer la prise en charge des SCA en vue de donner rapidement au patient son congé de l'hôpital ou d'entreprendre sans délai la prise en charge du SCA. Nous présentons ici une synthèse des publications sur le recours à l'apprentissage automatique pour le diagnostic des SCA.

Méthodologie : Nous avons effectué une recherche dans différentes bases de données, notamment PubMed, Embase et Web of Science, afin de recenser toutes les études répertoriées jusqu'au 13 janvier 2019 portant sur l'évaluation d'algorithmes d'apprentissage automatique pour le diagnostic des SCA chez les patients présentant une douleur à la poitrine. Nous avons ensuite utilisé des modèles de

Machine learning (ML) is a modern form of artificial intelligence by which a machine learns to perform tasks with exposure to large amounts of data.[1-4] The focus of ML is typically the development of algorithms that mathematically optimize the outcome without specific instructions. ML algorithms function by first exposing a computer to a training dataset. By means of various ML algorithms,[1-4] the machine is trained to perform the required task. Its ability is then tested against a new set of data: the validation set.[1-4] As the machine is exposed to more data, its ability to perform the required task becomes more refined.[1-4]

Acute coronary syndrome (ACS) is a common condition with important financial and societal effects.[5-7] Patients who present with symptoms suggestive of myocardial ischemia are often responsible for emergency room (ED) overcrowding.[5] The diagnosis of ACS can be particularly difficult.[6,7] Underdetection of ACS can be life threatening.[7] On the other hand, overdiagnosing ACS can lead to inappropriate and costly overuse of resources.

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values ranged from 0.64 to 1.0, and the negative predictive values ranged from 0.91 to 1.0. The positive and negative likelihood ratios ranged from 1.6 to 33.0 and 0.01 to 0.13, respectively.

Conclusions: The excellent sensitivity, negative likelihood ratio, and negative predictive values suggest that ML may be useful as an initial triage tool for ruling out ACS.

méta-analyse bivariée à effets aléatoires pour faire la synthèse des résultats des études.

Résultats : Nous avons retenu 9 études ayant évalué le diagnostic par apprentissage automatique chez 6 292 patients au total. La prévalence des SCA dans les cohortes évaluées allait de relativement rare (7 %) à fréquente (57 %). La sensibilité et la spécificité groupées s'établissaient respectivement à 0,95 et à 0,90. Les valeurs prédictives positives allaient de 0,64 à 1,0 et les valeurs prédictives négatives, de 0,91 à 1,0. Les rapports de vraisemblance positif et négatif allaient respectivement de 1,6 à 33,0 et de 0,01 à 0,13.

Conclusions : Les excellents résultats obtenus à l'égard de la sensibilité, du rapport de vraisemblance négatif et des valeurs prédictives négatives semblent indiquer que l'apprentissage automatique peut être utile comme outil de triage initial afin d'écarter le diagnostic de SCA.

Although detection of myocardial infarction (MI) has been facilitated with introduction of high-sensitivity troponins,[8] the diagnosis of ACS without myocardial damage (without elevation of serum troponin) remains subjective, and its accuracy remains highly dependent on the clinical skills of the ED health care professionals.[5] Application of a ML algorithm can make the initial ED assessment more objective and may expedite management of ACS for either early discharge or early initiation of ACS management.[9] We aim to evaluate the diagnostic value of various methods of ML for ACS by summarizing the published studies evaluating ML in patients who presented to the emergency department with symptoms of potential cardiac ischemia.

Methods

Search strategy

We retrieved all studies that evaluated mixed methods of ML for the diagnosis of ACS from inception up to January 13, 2019, in in the following databases: Embase, PubMed, Web of Science, and Cochrane Register of Diagnostic Test Accuracy Studies. We retained only studies in humans and did not impose any language restriction. We used the following key words: machine learning, artificial intelligence, artificial neural network (ANN), support vector machine (SVM), naïve Bayes, classification tree, ACS, MI, and chest pain. The MESH terms used were machine learning *or* artificial intelligence *or* artificial neural networks *or* support vector machine *or* naïve Bayes *or* classification tree *and* acute coronary syndrome *or* MI *or* chest pain. We also manually reviewed the references of all relevant articles to enhance identification of published ML research.

Inclusion criteria. We included all fully published studies that evaluated various methods of ML using available clinical data in patients who presented to the emergency department with symptoms suggestive of ACS.

Exclusion criteria. We excluded abstracts, prehospital studies of patients with chest pain and studies that evaluated ML in stable coronary artery disease (CAD). We did not include ML focusing only on 1 diagnostic test to identify patients with ACS (such as studies evaluating ML in electrocardiogram [ECG] and echocardiogram). We also excluded studies that did not use final discharge diagnosis of ACS as the reference test. We did not retain studies that did not report true positive, true negative, false positive, and false negative cases.

Methods of ML evaluated

ANN is a ML algorithm designed to mimic the human brain, with multiple layers of interconnected digital neurons adjusting the strength of their connections based on the input provided to optimize the output.[10,11] SVMs create decision boundaries or rules to classify data.[12] They perform well with high number of variables in the algorithm.[12] A classification tree is a flow chart with rules of input combinations for classification of a data point.[13] It handles categorical data adequately, and its output can be easily interpreted by following each branch of the decision tree.[13]

Index test. Algorithms generated by machine learning.

Test data. Binary variable: presence of ACS, yes or no.

Target population. Patients who present to the emergency department with symptoms suggestive of myocardial ischemia.

Target condition. ACS including MI with or without ST-segment elevation and unstable angina.

Reference test. Final discharge diagnosis of ACS (either from the emergency department or from the hospital, whichever occurred later).

Data extraction

Three reviewers (P.I., X.Z., and T.H). independently selected studies for inclusion, extracted data, and evaluated the quality of each study. Disagreements were resolved by consensus. We contacted the investigators of the original studies to obtain missing data. The senior author (T.H.) had full access to the dataset and took full responsibility for the integrity of the data.

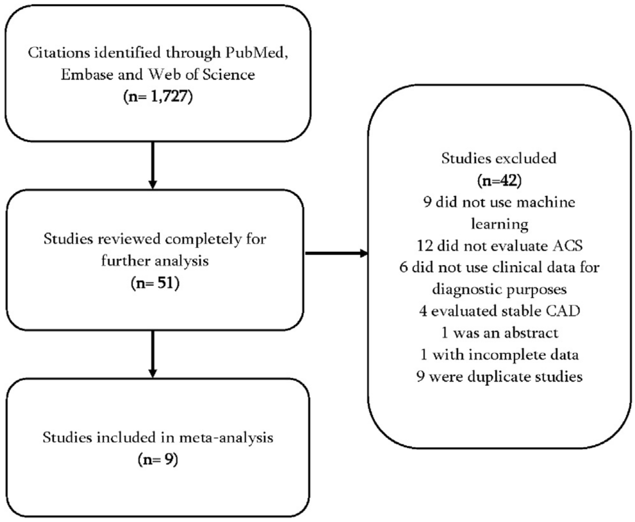

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow of study selection.

Assessment of methodological quality and risk of bias

Assessment for risk of bias and quality were completed by following the QUADAS-2[14] scale and GRADE. These evaluations were completed independently by 2 reviewers (T.H. and P.I.) (Supplemental Appendix S1). We ensured that this meta-analysis fulfilled all the criteria required in the **P**referred **R**eporting **I**tems for **S**ystematic Reviews and **M**eta-**A**nalyses (PRISMA) checklist.[15]

Statistical analysis

We calculated the diagnostic accuracy (predictive values and likelihood ratios) and diagnostic odds ratios of each ML approach. Due to the marked heterogeneity between studies (heterogeneity $\chi^2 < 0.001$ and $I^2 > 0.75$ with fixed model testing (Meta-DiSc 1.4), we elected to compute the diagnostic parameters by random-effect models and summarize the sensitivity and specificity by bivariate models (Review Manager [RevMan] Version 5.3. The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). We tested for publication bias by evaluating asymmetry of the linear regression plot of lnDOR against 1 per square root of effective sample size.[16] The parameters required to construct the summary bivariate curves and Deeks' publication bias were computed by SPSS version 24 (IBM, Armonk, NY).

Results

Selection of results

We describe selection of studies in Figure 1. We retrieved 1727 citations and reviewed 51 full studies. After exclusion of studies with duplicate and missing data, there were 9 studies[17-25] that fulfilled entirely our inclusion and exclusion criteria. We described their methodologies in Table 1 and the characteristics of the study populations in Table 2.

Ho Ha et al. were the only authors who did not use ANN as the main index test.[17] Their group evaluated hybrid data mining combining associations rules with classification tree and used ANN as the comparator test. All other authors used various types of ANN. Most authors[17,19-26] employed logistic regression as the comparator test. Only one group[17] compared ML with ED physicians' evaluations. The majority of patients were from single university centre emergency departments with the four largest studies[18-21]; 75% of the patients were from the United States and United Kingdom (Table 2). The mean age ranged from 53 years to 63 years, with the proportion of female patients ranging from 27% to 57% (Table 3).

Overall, the above methods of ML had excellent sensitivities, negative predictive values, and negative likelihood ratios (Table 4 and Fig. 2). The positive predictive values ranged from 0.64 to 1.0, and the negative predictive values ranged from 0.91 to 1.0. The positive and negative likelihood ratios ranged from 1.6 to 33.0 and 0.01 to 0.13, respectively.

The summary sensitivity and specificity were approximately 0.95 and 0.90, respectively (Fig. 3). The study by Green et al. was the obvious outlier, with a much lower specificity of 0.4 compared with the other studies.[22] The 95%

Table 1. Study characteristics

Studies	Publication Year	Sample Size*	Types of machine learning	Data input	Comparator test
Baxt	2002	2204	ANN with jackknife variance	40 variables: history, physical exam, ECG, troponin	ACI-TIPI, Goldman algorithm, logistic regression
Baxt & Skora	1996	1070	ANN	20 variables: history, physical exam, ECG	ED physician
Berikol	2016	228	SVM, ANN, naïve Bayes	History, physical exam, ECG, troponin and echocardiography	Logistic regression
Bulgiba	2006	887	ANN	Nine variables: history	Logistic regression
Green	2005	915	ANN with bagging, K-fold cross splitting	Eleven variables: history and physical exam	Logistic regression
Harrison	1991	150	ANN with multilayer perceptron	Ten variables: history and ECG	Logistic regression
Harrison & Kennedy	2004	1894	ANN with multilayer perceptron	Thirteen variables (history, physical exam, and ECG)	SVM, ANN
Ho Ha	2010	189	Hybrid data mining combining association rules and classification trees	37 variables (age, sex, and laboratory tests)	
Sprockel Diaz	2007	307	ANN	History, ECG, and cardiac biomarkers	

ACI-TIPI, acute cardiac ischemia time-insensitive predictive instrument; ANN, artificial neural network; ECG, electrocardiogram; SK, South Korea; SVM, support vector machine; UK, United Kingdom, USA, United States of America.

* Number of patients in the validation datasets.

Table 2. Characteristics of study populations

Studies	Country	Clinical setting	Consecutive enrollment	Endpoints evaluated
Baxt	USA	Single university centre	Not specified	ACS
Baxt & Skora	USA	Single university centre	Not specified	Myocardial infarction
Berikol	Turkey	Single university centre	Not specified	ACS
Bulgiba	Malaysia	Single university centre	Not specified	Myocardial infarction
Green	Sweden	Single university centre	Yes	ACS
Harrison	United Kingdom	Single university centre	Yes	Myocardial infarction
Harrison & Kennedy	United Kingdom	3 teaching hospitals	Not specified	ACS
Ho Ha	South Korea	1 hospital	Not specified	Myocardial infarction
Sprockel Diaz	Colombia	2 hospitals	Not specified	ACS

ACS, acute coronary syndromes.

Table 3. Characteristics of patients

Studies	Number of patients	Females (%)	ACS (%)	Mean age (standard deviation)	Diabetes mellitus (%)	Hypertension (%)	Coronary artery disease (%)
Baxt	2204	879 (39.9)	361 (16.3)	52.5 (13.9)	18.7	50.4	20.4
Baxt & Skora	1070	290 (27.1)	75 (7.0)	53.0 (NA)	NA	NA	NA
Berikol	228	NA	114 (50.0)	NA	NA	NA	NA
Bulgiba	887	233 (26.8)	246 (27.8)	53.8 (13.0)	NA	NA	NA
Green	915	403 (44.0)	190 (20.7)	69.8 (12.9) for ACS 60.8 (17.9) for no ACS	33.0	NA	NA
Harrison	300	NA	102 (34.0)	NA	NA	NA	NA
Harrison & Kennedy	1894	1036 (54.7)	843 (44.5)	60.1 (NA)	NA	NA	NA
Ho Ha	189	NA	97 (51)	NA	NA	NA	NA
Sprockel Diaz	92	52 (56.7)	52 (56.5)	62.7 (NA)	NA	NA	NA

ACS, acute coronary syndromes; NA, not available.

Table 4. Diagnostic values of individual study

Studies	Enrollment	Prevalence	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratios
Baxt	1999-2000	0.42	0.88	0.86	0.82	0.91	6.37	0.14	46
Baxt & Skora	NA	0.07	0.96	0.96	0.64	1.00	23.88	0.04	573
Berikol	2013	0.43	0.98	1.00	1.0	0.98	Undefined	0.02	10,101
Bulgiba	1999-2002	0.28	0.98	0.97	0.93	0.99	33.05	0.02	1578
Green	1997	0.21	0.95	0.40	0.29	0.97	1.59	0.11	13
Harrison	NA	0.34	0.88	0.88	0.79	0.94	7.28	0.13	54
Harrison & Kennedy	1992, 1995, 1996	0.45	0.92	0.92	0.90	0.93	11.11	0.09	126
Ho Ha	NA	0.51	0.99	0.97	0.97	0.99	30.35	0.01	2898
Sprockel Diaz	2012, 2013	0.57	0.96	0.78	0.85	0.94	4.27	0.05	86

NA, not available.

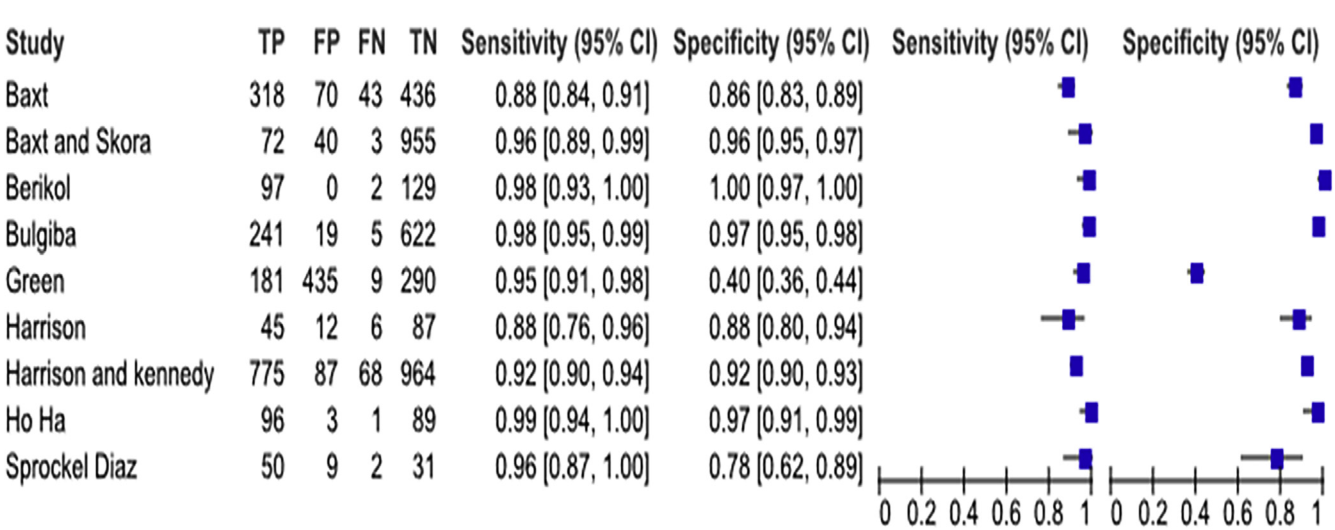

Figure 2. Paired forest plots of sensitivity and specificity.

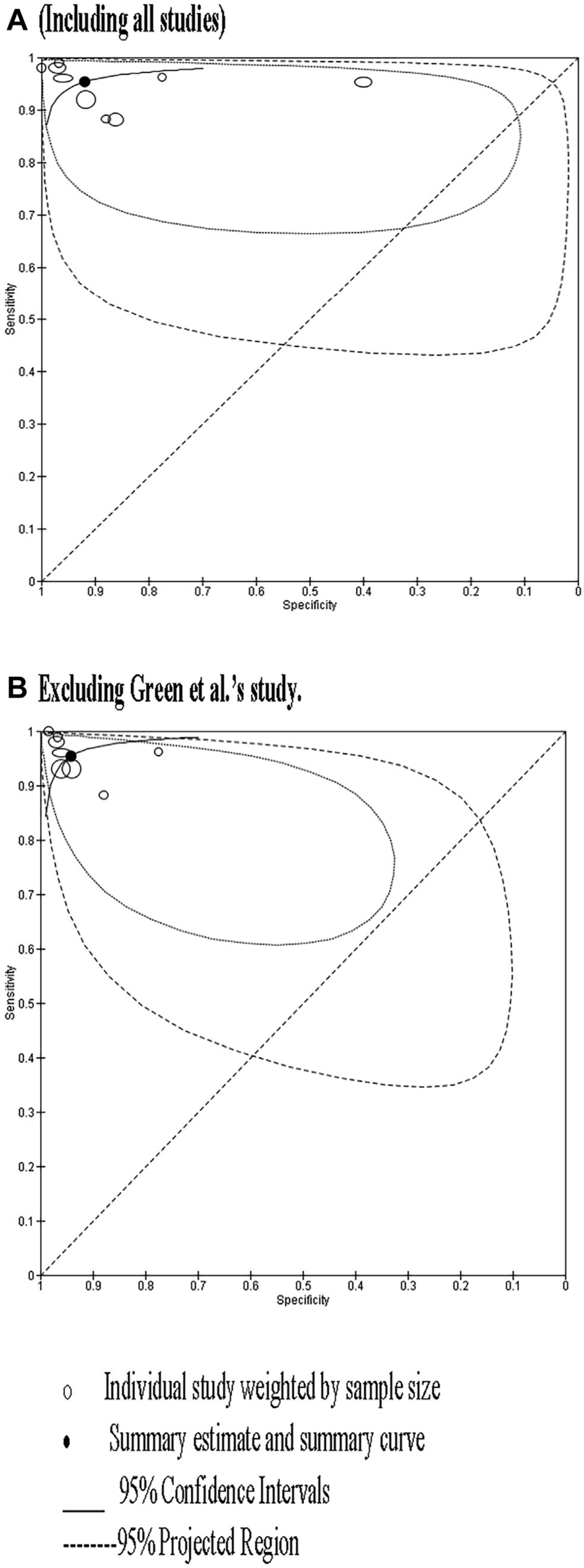

Figure 3. Summary receiver operating curve by bivariate model.

confidence intervals and projected regions of summary sensitivity and specificities narrowed with exclusion of the study by Green et al.[22] We evaluated the quality of the studies in Figure 4 and Supplemental Fig. S1. Overall, the studies had good applicability, with most cohorts enrolling patients with the target condition (potential ACS) and using the same reference test (final discharge diagnosis). The summarized evidence had a GRADE quality evaluation as moderate (based on the GRADE scale of very low to high) (Supplemental Table S1).

Discussion

To our knowledge, our meta-analysis is the first quantitative systematic review of various approaches of ML for the diagnosis of ACS. ML had excellent sensitivity and reasonable specificity within a wide range of populations. Furthermore, its excellent negative likelihood ratios and negative predictive values suggested that ML may be a useful add-on tool in the initial triage of patients with chest pain. As the specificity of ML, positive predictive value, and positive likelihood ratios were mainly fair, ML cannot be used at the present time to confirm the presence of ACS, but would be used mainly to rule out ACS.

The studies retained were marginally comparable, with marked heterogeneity in the populations, enrollment periods, methods, and endpoints of the studies included in our meta-analysis. The study populations originated from various countries with notable variations in the prevalence of ACS (ranging from 0.07 to 0.57). The enrollment periods ranged from 1991 to 2019. ML algorithms varied remarkably from a very parsimonious model, with only 9 variables obtained from history[23] to exhaustive collections of data from history, physical examination, and laboratory tests including echocardiography.[24] Despite being more comprehensive, the algorithms with more variables did not necessarily perform better than the more parsimonious models.

Although MI with ST-segment elevation can be generally easily diagnosed with an ECG, MI without ST-segment elevation requires elevation of troponins for confirmation. However, the first troponin is often normal. Consequently, serial troponin measurement is generally required with a minimum of 4 to 6 supplementary hours of ED stay. Can ML accelerate the identification of acute MI without requiring repeat troponin? Three studies[19,20,24] attempted to answer this question. All their algorithms had good specificity, negative predictive values, and negative likelihood ratios, even in cohorts with intermediate prevalence of ACS (>25%). This suggested that ML might be used to identify patients with very low probability of ACS who may benefit from early discharge from emergency departments without requiring serial troponin testing.

The various methods of ML evaluated above had superior diagnostic accuracies compared with ED physician and previous ACS scores.[18-20] Although Berikol et al.[25] and Baxt et al.[18,19] demonstrated superiority of ML to logistic regression, Green et al.[23] and Harrison and Kennedy[21] observed no significant difference between the diagnostic accuracies of ML and logistic regressions. However, aside from its potential use to create a risk score, logistic regression would not be a useful

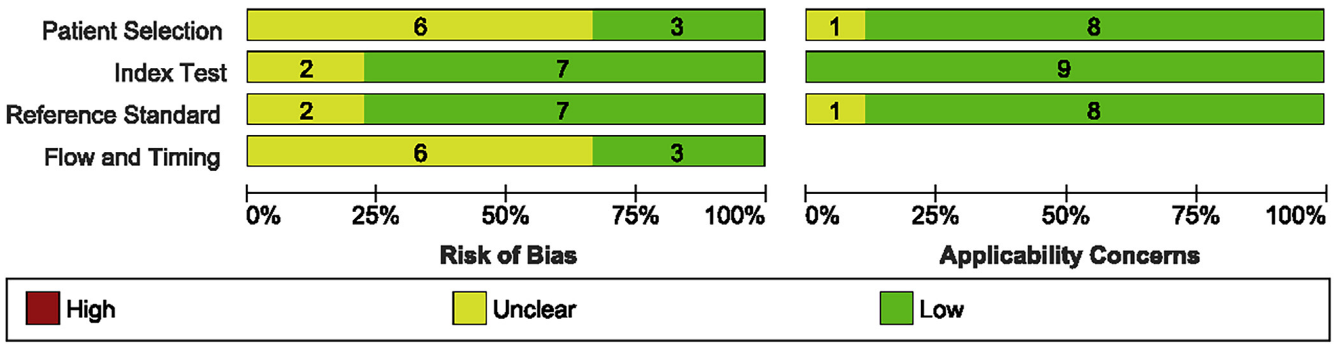

Figure 4. Quality methodological graph.

tool in the daily ED practice.[27] On the other hand, ML may be incorporated electronically eventually into patients' charts for rapid triage of patients with possible ACS.

The internal validity of our meta-analysis was enhanced by exclusion of case-control studies, as this design could potentially overestimate the accuracy of a diagnostic test.[28] In addition, the studies in our meta-analysis were not subject to verification bias, with all patients having the same reference test (final discharge diagnosis). Nevertheless, there is potential for selection bias due to the lack of specification of consecutive enrollment and incomplete description of study flow in several studies. This potential threat to internal validity may be due to incomplete reporting rather than true flaws of these studies.

With the increasing prevalence of electronic health records and "big data", there exists an incredibly large number of data that have the potential to train very powerful machines.[29] Most algorithms reviewed in our review were trained and validated on relatively small datasets. With larger datasets of more patients and variables, ML may become a very powerful and accurate tool for diagnosis of ACS. The algorithm would then continuously improve as it becomes exposed to new data. This may improve further the specificity and positive likelihood ratios so that ML may be used eventually to confirm (rule in) ACS so appropriate treatment can be initiated without delay.

Study Limitations

Our project had a few noteworthy limitations. First, the main limitation of our meta-analysis was that the retained studies used older methods of ML. Our systematic review could not identify studies of more contemporary ML technologies such as multilayer perceptron or deep learning. However, ANN and SVM (methods used in the retained studies) were still widely used in many medical applications, owing to their flexibility and requirement of smaller training datasets.[30] Second, most of our studies had relatively small number of patients, thereby limiting the accuracy of ML algorithms, which generally require a large number of data. Third, the diagnostic methods for ACS have evolved with the introduction of high-sensitivity troponins.[31] Therefore, our results may not be entirely applicable in this era of high-sensitivity troponins. Fourth, publication bias is a perennial threat for any meta-analysis of diagnostic tests.[16-28] Investigators tend not to publish report of a test with nonsatisfactory diagnostic values. It is highly possible that there may be instances in which ML may not have optimal diagnostic accuracies and therefore have not been published. However, there was no obvious asymmetry on the Deeks' plot to suggest significant publication bias (Supplemental Fig. S2). Finally, the internal validity of our meta-analysis relied heavily on the quality of the studies included. As there was incomplete reporting of methodology in several studies, the risk of significant bias cannot be ignored.

Conclusions

Considering its excellent sensitivity, negative likelihood ratio, and negative predictive values, ML may be useful as an initial triage tool to rule out ACS. With the increasing prevalence of "big data" electronic health records,[30] ML algorithms can be continuously refined, and its diagnostic accuracy may improve further with larger datasets of more patients and clinical variables. Refinement of current ML algorithms and technologies may further improve the specificity and positive likelihood ratios so that ML may be used to confirm (rule in) ACS to expedite appropriate treatment.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.09.013.