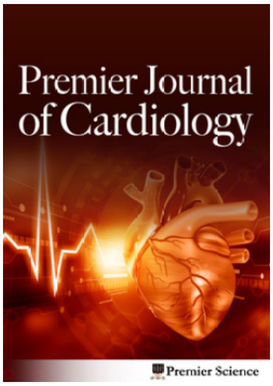

Using AI to Diagnose Myocardial Infarction: A Review of the Evidence Behind Machine Learning Application to the Emergency Chest Pain Patient

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ABSTRACT

Research into the application of machine learning to the diagnosis and risk stratification of patients presenting to the emergency department with undifferentiated chest pain has increased exponentially. Recent findings from the RAPIDxAI trial have brought into question the ability of these AI tools to improve patient outcomes. This review aims to place RAPIDxAI in the context of prior research, identifying current limitations to progress and opportunities for future research in the field. Although the RAPIDxAI trial has made progress toward assessing the clinical applicability of machine learning models, more work is needed to demonstrate the "real-world" benefits of such technology, particularly in their use as triage-based "rule-out" tools. Current research is limited by the lack of clear algorithm design information and the availability of validation protocols. Future research goals must focus on assessing the performance of currently validated tools across a broader range of metrics. Furthermore, research should continue to focus on areas of implementation beyond algorithm diagnostic sensitivity and specificity, including the human factors barriers to clinician acceptance and implementation.

Keywords: Artificial intelligence, Chest pain, Machine learning, Myocardial infarction

What This Review Adds

- RAPIDxAI represents a significant development in the clinical application of machine learning. Understanding these advances in the context of previous research is needed to identify the important steps this trial makes in pointing toward the direction of future research in the field.
- There is a broad history of research into the role of machine learning in chest pain presentations, with limited clinical application. Previous research has been held back by the lack of published algorithm protocols and design availability.
- Assessing the limitations of previous research reveals essential next steps for expanding the use of AI toward real-world clinical application. Further research should focus on assessing the impact of machine learning on broader patient outcomes, as well as the application of algorithms as "rule-out tools."

Introduction

Chest pain is one of the most high-risk undifferentiated presentations to the emergency department (ED). While the vast majority of patients with chest pain will be suffering from a benign condition, the risk of adverse events associated with missing a more severe condition is high.[1,2] Diagnostic uncertainty is relatively commonplace as clinicians undertake the difficult task of confidently identifying and differentiating serious pathologies like acute coronary syndrome (ACS) from relatively benign conditions such as musculoskeletal pain.[2] Errors in the timely identification and management of serious cardiac conditions can be catastrophic. As such, much research has focused on the development of tools and strategies to support clinicians in making these critical decisions.[3–5]

One proposed solution to answering this question of diagnostic uncertainty is to employ artificial intelligence (AI) and machine learning (ML) for diagnosis, management recommendations, and prognostication. As the role of AI in healthcare continues to expand at an ever-increasing rate,[6] it is important to review the current evidence base and identify strengths, limitations, and areas for future study.

This review focuses on assessing the availability of high-quality research on the role ML models can play in assisting with the diagnosis, prognostication, and management of chest pain presentations to the ED. The following article will consider recent developments in the field (specifically the completion of the RAPIDxAI trial)[6–8] alongside the broader context of our existing academic knowledge base. We will discuss the strengths and limitations of current research, identifying critical areas for future development.

Background

Chest Pain

The Global Burden of Disease study has sought to track worldwide trends in mortality and disability since its inception in 1990.[10] During this time, cardiovascular disease (CVD) has consistently been identified as the leading cause of death worldwide. In 2021, an estimated 19.4 million worldwide deaths were attributed to CVD. Of this, ischemic heart disease was by far the most common constituent cause.[11]

Chest pain as a presenting symptom is thought to account for 5–12% of all ED attendances.[12] However, one study estimates that ACS (composed of myocardial infarction [MI] and unstable angina) was responsible for less than a third of these presentations.[13]

Timely treatment of ischemic myocardial events is crucial for restoring organ function, reducing long-term disability, and ultimately preventing death. Assessment of the chest pain patient with a suspected cardiac cause generally consists of a detailed history, physical examination, electrocardiogram (ECG), non-invasive imaging, and interpretation of biochemical test results

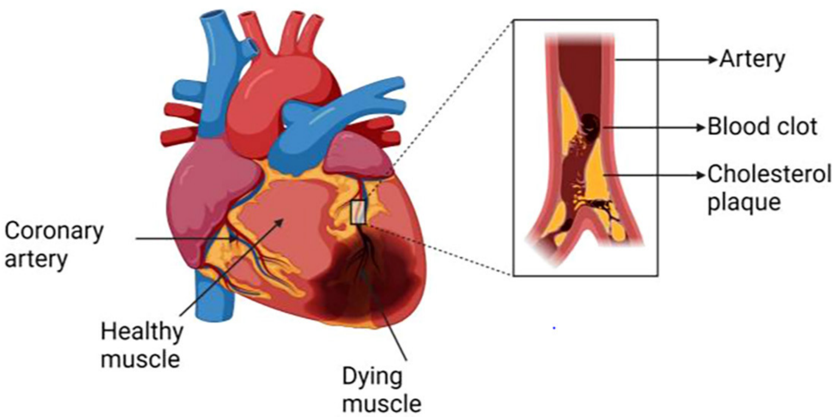

Fig 1 | Advancements in AI for precision diagnosis and treatment of MI: A comprehensive review of clinical trials and randomized controlled trials[20]

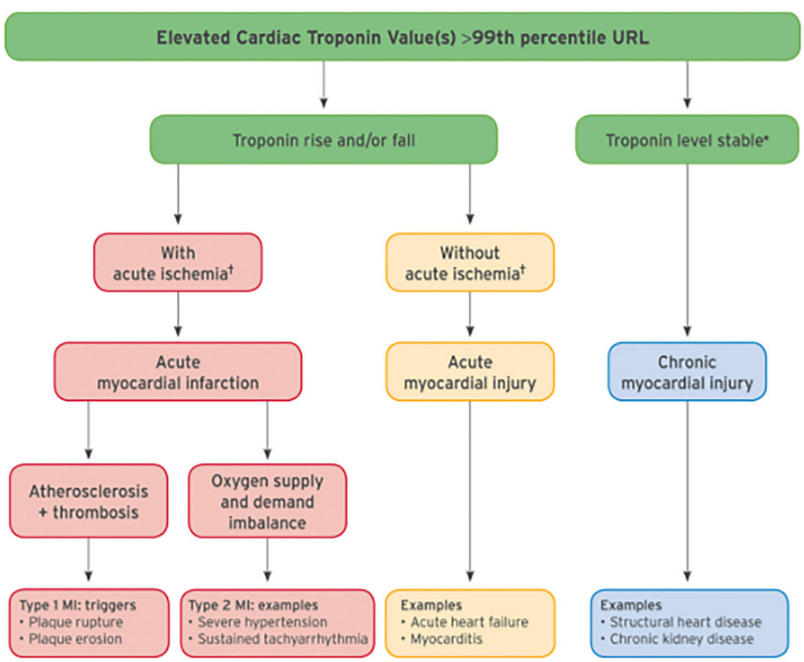

Fig 2 | Fourth universal definition of MI (2018)[16]

(specifically cardio-biomarkers such as high-sensitivity troponin).[14] At this point, clinicians must make use of guidelines and their own clinician judgment to form a differential diagnosis that guides the next steps in management, including considering the use of invasive imaging (Figure 1).

When MI is suspected, clinicians still face significant challenges in identifying the correct diagnosis and associated management plan. The fourth definition of MI (2019) seeks to provide an international standardization to the definitions used to describe MI and its associated conditions.[15,16] Some important definitions include:

- Myocardial Injury: Evidence of elevated cardiac troponin values above the 99th percentile reference values. This is considered acute if there is a rise and fall in these values.
- MI: Acute myocardial injury with clinical evidence of acute ischemia. Clinically, this presents as a rise and fall in cardiac troponin values plus at least one of the following:
  - Symptoms of myocardial ischemia
  - New ischemic ECG changes
  - Pathological Q waves
  - Imaging evidence of an ischemic myocardium
- Type 1 MI: MI caused by atherosclerotic coronary artery disease (usually as a result of plaque disruption).
- Type 2 MI: MI caused by ischemic myocardial injury as a result of a mismatch between oxygen supply and demand (unrelated to acute coronary artery atherothrombosis) (Figure 2).

At this point, it is worth considering the difficulty in clinically differentiating between Type 1 and 2 MIs. Although each falls into generally recognizable patterns in presentation and investigation results, it is not uncommon for one condition to mimic the other (requiring invasive investigation to determine the presence of an atherosclerotic plaque).

Importantly, management differs greatly between these conditions. Type 1 MIs (those involving atherosclerotic plaques) are primarily treated by percutaneous coronary intervention (PCI), an invasive procedure with associated procedural risks. This is in contrast to Type 2 MIs and other causes of myocardial injury, each of which requires distinct medical management (for instance, prescribing anti-platelet or anti-mineralocorticoid therapy).[14] Such medical management is inadequate for optimally treating Type 1 MI atherosclerotic plaques. It is within this area of diagnostic uncertainty and markedly different management strategies that recent developments in the use of AI seek to support clinician decision-making and improve patient outcomes.

Understanding AI

Before considering its application to cardiology, care must be taken to understand the terminology used to describe various aspects of AI.[17]

- AI: A broad term that describes the ability of computers to use information to solve problems or perform tasks commonly associated with human actions.
- ML: AI that involves the computer being able to learn and adapt without explicit human-initiated instructions by drawing inferences from data patterns.
- Deep Learning (DL): An extension of machine learning that uses complex "neural networks" to learn from vast data sets, more closely resembling "brain-like" functions (Figure 3).

Despite the increased awareness of the application of AI technologies among the general public being a

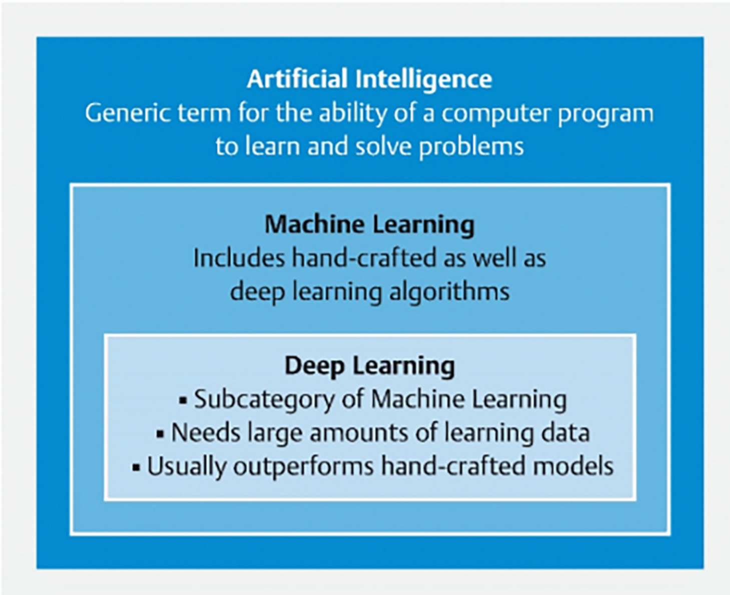

Fig 3 | A technical review of AI as applied to gastrointestinal endoscopy: Clarifying the terminology[17]

relatively recent phenomenon, research regarding its application to medicine has been ongoing for a significant period of time.[18,19]

- The 1960s saw the emergence of early command-following robots and language-responsive chatterbots that would form the foundations of later AI applications to medicine.
- Across the 1970s, several programs were developed for use in narrow medical applications, using patient data to suggest potential diagnoses and recommend management plans for certain clinical presentations.
- 1986 saw the development of the DXplain system, a comprehensive differential diagnosis program, largely for medical education purposes.
- The 2010s onwards have seen a rapid development in the use of DL to develop computer-assisted diagnosis programs, particularly in assisting the interpretation of radiology imaging.

Advances in research into using AI to aid diagnosis, prognostication, and management of chest pain in the ED have also included some significant milestones.[20]

- In 1990, researchers trained an artificial neural network to differentiate between patients presenting with acute MI, demonstrating improvement on other established analytical approaches.
- A 1996 paper demonstrated a statistically significant improvement in the performance of a trained neural network in identifying MI when compared to physician performance.
- Than et al.'s 2019 paper described the use of the "MI3 clinical decision tool," using complex ML to diagnose Type 1 MI with an exceptionally high sensitivity and specificity.

The Recent RAPIDxAI Trial

Trial Background

One of the latest developments in the use of ML in emergency chest pain presentations was the successful completion of the RAPIDxAI trial in 2024.[7–9] The researchers outlined their approach and results in a presentation to the European Society of Cardiology on the 2nd of September 2024.[21]

The study aimed to bridge the gap between the current academic understanding of the role AI can play and clinical application by using ML to determine which chest pain patients are most appropriate for invasive management (i.e., PCI) in the context of a positive high-sensitivity troponin result. Importantly, researchers wanted to know not only if the algorithm could identify these patients but whether this would ultimately lead to improved clinical outcomes.

Previous trials sought to train and validate the ML algorithm used in the study.[22,23] Researchers used electronic health records, including patients with suspected ACS, to train and test an ML algorithm. This included developing two diagnostic prediction models to distinguish between myocardial injury and infarction and subsequently between Type 1 and 2 MI (according to the fourth universal definition).[15] This was further supported by the development of an event prediction model for a 30-day risk of MI or death.

A cluster randomized control trial (RCT) was then undertaken, involving 12 Australian state hospitals (six randomized into the active arm, six into the control arm). The study enrolled 14,131 patients presenting to EDs with chest pain. Of these, 3029 patients were entered into the intention-to-treat (ITT) analysis on the basis of a positive high-sensitivity troponin result with a suspected cardiac cause. Clinicians treating patients in the active arm (1568) were provided with a probability of Type 1 MI and treatment recommendation by the ML algorithm based on provided patient data points. Clinicians could then choose to use this information to guide their clinical decision-making. The primary measures of interest were cardiovascular mortality, MI, or unplanned cardiovascular readmission in the subsequent 6 months, with a safety end point of all-cause mortality or MI within 30 days.

The ITT analysis revealed no difference between the active and control arms, meaning ML did not impact the primary measures of interest or safety end point. However, the study did provide some interesting results with implications for future clinical applications. Patients classified by the algorithm as not having a Type 1 MI were 47% less likely to undergo PCI when compared to the control arm. In the context of non-inferior patient outcomes, this represents a significant improvement in care, avoiding a procedure with associated risks and resource implications. Equally, patients were more likely to be prescribed medical management (statins, anti-platelets, and mineralocorticoid inhibitors), which was in line with non–Type 1 MI management guidelines.

Trial Discussion

The RAPIDxAI study ultimately demonstrated no direct benefit to patient outcomes from the implementation of an AI tool to assist diagnosis in chest pain presentations to the ED. This finding is interesting as it deviates from the trend seen in similar research over the last couple of decades, which largely report meeting their primary outcomes. There has long been a suspicion that research involving the clinical application of AI suffers from the same issues around publication bias as other fields of medicine, where positive studies are selectively published or outcomes likely to produce a positive result are set.[24] This trial provides important insights into the limitations of current AI abilities and the likelihood of being able to provide real-world clinical benefits and improve patient outcomes.

It is worth considering why this AI algorithm (already validated at a comparable or improved level of sensitivity and specificity vs expert clinicians)[22] did not see a statistically significant improvement in outcomes. One possibility to consider is that the resultant changes in patient management itself do not lead to better outcomes. Clinicians are more likely to over-triage and go ahead with invasive investigation rather than risk the harm caused by missing a Type 1 MI when the clinical picture is uncertain. Indeed, this theory is supported by the secondary findings that in the AI-assisted intervention arm, patients were less likely to undergo PCI and more likely to be solely managed using pharmacological interventions. Importantly, this appears to not have led to worse outcomes for patients, proving the ability of this AI tool to provide clarity in diagnostic uncertainty and allow clinicians to safely avoid unnecessary PCI. To further solidify this claim, future research should consider broadening the assessment of harm-based outcomes over a longer period of time, particularly looking to include assessments of intervention (both invasive and drug-based) harm or incidents between an AI-assisted cohort and a control group. A large multicenter randomized control trial that includes this outcome metric has the potential to significantly contribute to advancing AI-assisted diagnosis in chest pain presentations toward widespread clinical application.

Furthermore, the resource implications of these findings should be considered. For PCI, reducing the burden of unnecessary invasive investigations can represent a huge cost-saving for hospitals. The value of clinician time saved also cannot be understated. AI-assisted diagnosis technology used in this setting can free up valuable catheter lab space and reduce the time spent by cardiology specialists in the ED, improving the availability of downstream, non-urgent intervention and care. This aligns with similar resource-saving benefits that have been seen with the introduction of AI into other areas of medicine.[18,25]

Another possible reason for not seeing changes in patient outcomes in this trial was noted by the authors. Clinicians in the intervention arm were not forced to follow the recommendations laid out by the algorithm. Indeed, most clinicians report not using the tool as the primary driver of their diagnosis and management plan but rather as a "safety net" for their decisions. There is strong evidence from other research in the field that despite using models that are validated to have an equal or higher sensitivity and specificity for diagnosis than expert clinicians, they are very reluctant to rely on these tools.[26] The authors of this study suggest an opportunity for future research, evaluating patient outcomes between an AI-assisted intervention arm with management initiated by non-senior decision-makers (nurses and more junior medical staff) compared to a control arm of usual expert cardiologists and senior ED decision-makers.

However, this theory can, at least in part, be refuted by the fact that management was indeed significantly different between the two groups and, as such, did have an impact on the behavior of senior decision-makers. Future research into the role non-experts have in AI-assisted diagnosis would help provide much-needed clarity and open up a new door toward real-world clinical application. We are likely to see further insights into the trial's strengths and limitations on full publication.

Other Studies Exploring Machine Learning in Chest Pain Presentations

Stewart et al. 2020

Of course, it is important to place the RAPIDxAI study in the context of previous research. One paper that provides an excellent insight into the field is the 2020 systematic review "Applications of machine learning to undifferentiated chest pain in the ED: A systematic review."[24]

The authors used a comprehensive search strategy to identify a total of 23 retrospective or prospective studies that applied an ML technique to undifferentiated adult chest pain presentations to the ED. This search identified a broad range of research from 1990 to 2020. Some key papers included:

- In 1990, Baxt published a retrospective single-center analysis on the use of an artificial neural network to diagnose occlusive ACS in chest pain presentations.[27] The algorithm performed substantially better than the performance of other analytical approaches or physicians. This provided some of the earliest evidence of the high levels of diagnostic sensitivity and specificity seen in ML models.
- Hollander et al. published a 2003 paper that assessed changes in admission behavior and clinician management plans following the implementation of an artificial neural network to support admission or discharge decisions.[28] This study found that the use of this tool did not change admission rates or clinician management plans, likely as a result of a decision having already been made by clinicians prior to the availability of cardiac biomarker results used by the algorithm to provide a relatively late decision. This article highlighted some of the emerging challenges of AI application in a real-time clinical setting.
- In 2014, Liu et al. used ML to identify the most relevant variables in predicting adverse events associated with chest pain presentations in the ED.[29]

The ML algorithm was able to identify multiple valuable indicators that, when assessed together, could improve the prediction of events. However, the authors noted that more variables did not necessarily guarantee better prediction results. With the development of increasingly complex ML algorithms, this study highlighted the importance of developing targeted algorithms using limited and validated data points to improve performance.
- Than et al. reported on the use of the “MI3 clinical support tool.”[30] Their 2019 paper on the use of the MI3 tool to provide a risk of Type 1 MI based on high-sensitivity troponin and patient demographic information improved the identification of high- and low-risk patients, supporting better early clinical decision-making. The tool outperformed the European Society of Cardiology 0/3-hour pathway[31] standard practice. This article demonstrated the utility of ML in early triage and risk stratification, providing a promising potential for clinical application.

Stewart et al.’s 2020 systematic review provides a comprehensive insight into the evolution and direction of research into ML use for chest pain presentations. The review identifies several important areas of research limitation that are worth considering. Firstly, the authors describe the limited extent of research looking at direct real-world application, with the vast majority of papers focusing on ML model diagnostic specificity and sensitivity or adverse event outcomes. While these do provide fundamental building blocks for the theoretical clinical applicability of such tools, further work is needed to evaluate them in practice.

The RAPIDxAI trial makes substantial progress in this area, assessing patient outcomes in a real-world application.

Both the RAPIDxAI trial and Stewart et al.’s systematic review identified the need to look at evaluating clinician acceptance of the use of such tools in practice. Interestingly, Stewart et al. point out the impressive abilities of ML models that do not incorporate many data points routinely used by clinicians in the diagnosis and management work-up of potential Type 1 MI patients. For example, not one study used DL natural language processing abilities to incorporate the use of free text to assess patient histories or clinical notes. Again, this opens up the possibility for future research to focus on incorporating natural language processing into ML algorithms. However, with previous studies suggesting that increasing the number of data points used may not improve algorithm performance,[29] it is unclear if such advances would provide actual clinical benefits.

Finally, the 2020 systematic review discusses the high risk of bias and low clinical applicability of research into ML algorithm use in undifferentiated chest pain patients. Of the 23 papers included, only three studies were considered to have a low risk of bias and a high clinical applicability. Only four studies externally validated their ML algorithm, and only one study used a previously published or registered protocol. Furthermore, only two of the included studies did not publish positive results, raising the possibility of significant reporting bias in this field of research.

Studies from 2020 Onward

Further advances have been made in the field between the systematic review publication and the most recent RAPIDxAI trial. The author used a basic PubMed® search strategy and abstract screening to identify 22 publications of potential interest (a protocol of this basic search strategy is available in Appendix 1). The majority of studies focused on the sensitivity and specificity of ML algorithms in diagnosing MI, mirroring the findings of Stewart et al.’s systematic review. Some papers of note that researched other applications of ML include:

- White et al.’s 2021 paper explored the capability of AI to assist in the exclusion of coronary atherosclerosis during Coronary Computer Tomography Angiography (CCTA) in the emergency setting.[32] The algorithm supported rapid and accurate identification of plaque presence, reducing the burden of specialist image interpretation and revealing the potential for AI-assisted CCTA for quick rule-out in the ED.
- In 2023, Nyström et al. found that the integration of previous ECG images into an ML algorithm assessment of risk for patients presenting to the ED with chest pain did not improve its accuracy.[33] This goes against current best practice recommendations for manual ECG interpretation and reaffirms previous research that indicates increased data points do not lead to improved algorithm performance.
- Zworth et al.’s 2023 systematic review assessing the diagnostic abilities of ML-assisted ECG interpretation for Type 1 MI diagnosis highlighted the higher sensitivity but lower specificity of such tools when compared to clinicians.[34] This reaffirms the role of AI in “safety netting” clinical decisions but refutes the claim of superior overall performance when compared to clinicians.
- In 2024, Toprak et al. published a retrospective study on the use of ML to assist with the interpretation of point-of-care high-sensitivity troponin to rule out MI.[35] The ML algorithm was found to outperform the current guideline-based rule-out process, supporting its use in early, safe triage decision-making.

Discussion

The Strengths of Current Research

The rate of research into the role ML can play in acute chest pain presentations is increasing exponentially. Various models have consistently demonstrated a high sensitivity when it comes to identifying Type 1 MI, with many tools showing a promising level of specificity as well. A strong evidence base has been developed to determine which data points provide the most accurate AI-driven diagnosis. ML models have also been shown to provide accurate information on the risk of adverse events across multiple patient groups. Taking these advances in research together, it is clear that we now have the capability to use ML to augment clinician decision-making, providing supplemental information and a potential rule-out tool to stretched front-line clinicians. We have also begun to see an increase in studies evaluating the real-world clinical applicability of such technology. The RAPIDxAI trial and other similar recent papers have sought to evaluate patient outcomes and provide the necessary link to clinical practice. So far, the picture is mixed regarding the outcome-driven utility of these tools, and such findings indicate the need for further research in this area.

Recent studies have also sought to diversify the approach to ML use in chest pain presentation beyond its diagnostic utility. The introduction of ML to improve the rule-out capability of laboratory results and imaging studies can support clinician decision-making, promote safe medical management or discharge, and ensure the effective use of limited resources.

The Limitations of the Current Research

Stewart et al. identified several limitations in the current research that still remain applicable to the progress made in the field today. There is still a lack of validated models that have undergone training on sufficiently large data sets. As evidence demonstrates the improved accuracy of ML algorithms when trained using larger data sets, committing resources to creating ever more accurate models becomes increasingly important.

As previously discussed, there is limited research into the human factors that surround the clinical applicability of ML. This limitation was acknowledged in both the Stewart et al. systematic review and by the researchers in the RAPIDxAI trial. As accurate models show increasing promise in clinical applicability, research must be undertaken to understand the human factors barriers to the successful implementation of such technology. One such theorized hesitance from clinicians comes from the "black-box" design of ML algorithms, where a lack of transparency on how the algorithm provides a recommendation makes it difficult for clinicians to base their decision-making on such tools.

Similarly, current research is somewhat limited by the availability of in-depth protocols and algorithm training information. Most ML models are obscured by concerns over sharing proprietary information on the AI design. As such, research reproducibility has been significantly hampered. Many high-quality studies require several years to design, train, validate, and test their own models before questions of clinical applicability can even be studied. This has led to a bottleneck delay, where studies on diagnostic sensitivity and specificity are abundant. However, research into specifics of clinical application and the effect on patient outcomes is limited.

Finally, although early research demonstrated high levels of ML algorithm diagnostic sensitivity and specificity, more recent studies provide significant limitations to this claim. As models are employed across a wider variety of clinical applications (for instance, in augmenting ECG and troponin interpretation), studies have consistently demonstrated a far superior sensitivity than specificity, solidifying their utility as rule-out tools. The RAPIDxAI trial provides important context that even when ML algorithms perform well, this may not necessarily translate into improved patient outcomes.

Next Steps

With the increasing exploration of AI's clinical applicability for patients presenting with undifferentiated chest pain, there is huge potential for the introduction of real-world ML usage. Future studies should focus on the following:

- Training and development of ML algorithms on huge data sets, assessing diagnostic sensitivity and specificity alongside the impact on patient outcomes.
- Further research into the impact human factors may have on the successful adoption of ML algorithms into practice.
- Assessment of the impact of ML "rule-out" tools on patient outcomes at the triage stage.
- Long-term, multicenter randomized controlled trials that investigate expanded patient outcome measures. For example, the impact of ML on 1-year adverse events or procedure-associated risk reduction. This may include further consideration of the impact ML can have on resource allocation and availability.
- With the increasing evidence base on ML tool diagnostic sensitivity and specificity for Type 1 MI, there is an opportunity for the publication of a meta-analysis that employs a sufficiently powered quantitative synthesis to provide new high-level evidence to the field.

Conclusion

In summary, this review identifies a broad history of research into the use of ML for patients presenting with chest pain in the emergency setting. The recent RAPIDxAI trial appears to deviate from the trend of ML superiority by not demonstrating a direct impact on patient outcomes. However, the study does provide some of the strongest evidence for the safety and positive resource implications in a real-world clinical setting. By understanding the progress made in the RAPIDxAI trial in the wider context of ML research in the field, we are able to draw strong conclusions on the direction of future research, as well as the associated limitations and challenges we may face.

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Appendix

Appendix 1 — PubMed® Search Strategy

(("Artificial Intelligence"[tiab]) OR ("Machine Learning"[tiab])) AND (("Chest Pain"[tiab]) OR (MI[tiab]) OR ("Myocardial Infarction"[tiab]) OR (ACS[tiab]) OR ("Acute Coronary Syndrome"[tiab])) AND ((ED[tiab]) OR ("Emergency Department"[tiab]) OR (ER[tiab]) OR ("Emergency Room"[tiab])) AND ((fft[Filter]) AND (2020:2025[pdat])) Filters: Full text