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Review Article

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Using Cardiac Magnetic Resonance Imaging to Evaluate Patients with Chest Pain in the Emergency Department

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ABSTRACT

Chest pain is one of the most common presenting symptoms in the emergency department (ED). Among patients with abnormal troponins, it is imperative to quickly and accurately distinguish type 1 acute myocardial infarction (AMI) from other etiologies of myocardial injury. Although high-sensitivity troponin assays introduced a high negative predictive value for AMI, they have exposed the need for diagnostic modalities that can determine the etiology of acute myocardial injury. Cardiac magnetic resonance imaging (CMR) is an effective tool to risk stratifying chest pain among patients in the ED. CMR is non-invasive and has a lower cost of care and shorter length of stay compared to those of invasive coronary angiography. It also provides detailed information on cardiac morphology, function, tissue edema, and location and pattern of tissue damage that can help to differentiate many etiologies of cardiac injury. CMR is particularly useful to distinguish chest pain due to type 1 AMI versus supply-demand mismatch due to acute cardiac noncoronary artery disease. A detailed review of the literature has shown that CMR with stress testing is safe to use in patients presenting to the ED with chest pain, with or without abnormal troponins. CMR is a useful, safe, economical, and effective alternative to the traditional diagnostic tools that are typically used in this patient population. It is a practical tool to risk-stratify patients with possible cardiac pathology and to clarify diagnosis without invasive testing.

Keywords: Magnetic resonance imaging; Cardiology; Chest pain; Emergency service, hospital; Troponin

INTRODUCTION

Chest pain is one of most common presenting complaints in the emergency department (ED), accounting for over 6.5 million encounters in the United States (US) in 2017.[1] Acute myocardial infarction (AMI) is an important cause of death. Therefore, rapid and accurate diagnosis of AMI is critical to initiate effective evidence-based medical management and early revascularization.

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Author Contributions

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High-sensitivity cardiac troponin (hsTn) assays have been recently introduced and are a cornerstone of diagnostic testing in patients with chest pain. These new assays have very high negative predictive values ranging from 95% to 100% for ruling out acute myocardial injury from AMI.[2] Cardiac troponins are structural proteins unique to the heart and are sensitive markers of cardiomyocyte necrosis. Although troponins indicate acute myocardial injury, they are not specific to etiology. Myocardial injury can result from AMI or due to other processes that cause supply-demand mismatch. Therefore, the positive predictive value of hsTn for diagnosis of AMI is limited, ranging from 19% to 83% in a large multicenter clinical trial.[2] In real-world observational data, however, the prevalence of true type 1 AMI among patients presenting to the ED initially suspected to have acute coronary syndrome (ACS) without ST-segment elevations on electrocardiogram (ECG) was 4.2%, with a positive predictive value of hsTn as low as 16%.[3] Quite commonly, a patient presents with chest pain and cardiovascular risk factors but has an ECG without ST-segment elevation. In this situation, it is difficult to differentiate type 1 AMI (due to coronary plaque rupture) from acute cardiac noncoronary artery diseases (CNCDs) such as hypertensive urgency/emergency, acute inflammatory or infiltrative disease, pericarditis, takotsubo, hypertrophic or other cardiomyopathy, acute heart failure, and cardiac arrhythmias cause myocardial injury from demand-supply mismatch in myocardial blood flow (i.e., type 2 AMI or myocardial injury not related to ischemia).

Clinicians have examined the utility of absolute hsTn values and changes over time to distinguish AMI from CNCDs but have had limited success. Early invasive coronary angiography (ICA) is performed frequently in patients with abnormal hsTn. Even in patients who are possibly suffering from myocarditis or takotsubo cardiomyopathy, the risk of missing AMI requiring revascularization outweighs the procedural risk and associated cost.[4] Registry data from the US (ACTION Registry/National Cardiovascular Data Registry) and Europe have shown that, of patients with non-ST elevation myocardial infarction (NSTEMI) and troponin elevations using standard assays, more than 70% undergo invasive angiography, but only about 40% eventually need revascularization for significant coronary artery disease (CAD).[5] With increasingly sensitive assays, the number of patients suspected to have AMI will increase, leading to more hospital admissions and coronary angiography procedures that significantly increase health care cost and hospital bed utilization.[6]

The increasing utilization of hsTn increases the need for new diagnostic pathways to better stratify ED patients who present with chest pain and have mildly abnormal hsTn with inconclusive ECG findings. Ideally, clinicians should be able to differentiate patients with structural heart disease that require specific therapies (including cardiomyopathy, inflammatory disease, acute heart failure, and even AMI if unrecognized initially) involving hospital admission from those with myocardial injury without a structural correlate (type 2 AMI). Those with type 2 AMI might require hospital admission and therapy for the underlying condition on a non-cardiology service or might be able to be safely discharged from the ED with outpatient follow-up. One differentiation strategy is to use noninvasive cardiac imaging with cardiac magnetic resonance imaging (CMR) in the ED.[7]

In this article, we review the use of CMR in patients presenting to the ED with acute chest pain. We discuss the feasibility and safety of CMR for early diagnosis. Finally, we examine its use as a gatekeeper for hospital admission and coronary angiography in the heterogenous patient population of those presenting with chest pain and mildly abnormal hsTn in whom the diagnosis remains unclear after initial evaluation with ECG and clinical history.

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RATIONALE FOR USE OF CMR IN PATIENTS WITH CHEST PAIN AND ABNORMAL HIGH-SENSITIVITY TROPONIN

The accurate diagnosis of type 1 AMI, type 2 AMI, or non-MI causes of elevated hsTn is imperative because the management is significantly different. Treatment with type 1 AMI therapies can be potentially harmful in a type 2 AMI scenario (e.g., intravenous heparin in hypertensive urgency).

CMR can be applied to a variety of clinical scenarios. Different techniques can be used to assess global and regional function with cine imaging. For instance, T2-weighted imaging can be used to assess myocardial edema, stress, and rest perfusion imaging to evaluate myocardial ischemia after infusion of vasodilator agents (adenosine, regadenoson, or dipyridamole). Delayed-enhancement CMR can be used to assess the presence and pattern of myocardial necrosis, inflammation, or infiltrative disease. Ancillary techniques for tissue characterization (e.g., T1 parametric mapping for infiltrative disease, T2*-imaging for iron overload), velocity flow mapping for valve assessment, and tomographic images for chest morphology can be deployed as clinically indicated.

CMR is considered a key diagnostic test in patients with "MI with non-obstructive coronary arteries" (MINOCA).[8] The presence of regional wall motion abnormalities in a typical coronary distribution territory accompanied by tissue edema and subendocardial late gadolinium enhancement (LGE) in a patient with acute chest pain and abnormal hsTn is highly sensitive and specific for diagnosis of AMI.[9] Even if all universal definition criteria for a type 1 AMI are met, 5% to 20% of these cases can have MINOCA. Possible mechanisms of MINOCA include plaque disruption, thrombosis, thromboembolism, superimposed vasospasm, myocarditis, takotsubo cardiomyopathy, or a combination of these processes.[8][10] However, because the coronary arteries can look normal or near normal at the time of angiography, the ischemic mechanism of myocardial necrosis might not be appropriately identified; therefore, important secondary prevention therapies (such as antiplatelet agents and statins) will not be instituted. Although CMR cannot differentiate between the mechanism of ischemic injury in MINOCA (i.e., spasm versus emboli), it can identify ischemic injury and differentiate it from myocarditis, takotsubo cardiomyopathy, or other forms of acute CNCD. Without information from CMR, the absence of epicardial stenosis of the ICA in a patient with abnormal troponins does not identify the mechanism of injury. CMR is needed to differentiate true ischemic injury ("True" MINOCA) from myocardial injury that is not related to ischemia from acute CNCDs ("False" MINOCA).

In the following paragraphs, we briefly discuss how CMR provides information on morphology, function, tissue edema, and location and pattern of tissue damage to identify some of the more common etiologies of acute myocardial injury not related to ischemia.

Myocarditis leads to (1) dysfunction that is not typically confined to a coronary distribution territory, with (2) myocardial edema and (3) necrosis. The diverse pathophysiology of acute viral myocarditis, the post-viral autoimmune responses, and the high prevalence of vasospasm explain the typical findings of epicardial or patchy focal LGE sparing the endocardium.[11] Of note, subepicardial inflammation can also accompany pericarditis in as many as 49% of cases, which is referred to as myopericarditis.[12] Aside from viruses, other etiologies of inflammatory disease of the myocardium include eosinophilic myocarditis,[13] cardiac sarcoidosis,[14] or immune checkpoint inhibitors.[15]

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Takotsubo cardiomyopathy typically demonstrates transient hypokinesia, akinesia, or dyskinesia of the left ventricular (LV) mid-segments with or without apical involvement, extending beyond the typical coronary territories, with edema but little to no LGE on routine studies.[16]

Acute heart failure with reduced or preserved LV ejection fraction in patients with prior or new onset of symptoms can present with chest pain, abnormal hsTn, nonspecific ECG changes, and renal disease or other confounding factors for myocardial injury.[17] Patients with unrecognized cardiomyopathy, such as hypertensive heart disease/cardiomyopathy, hypertrophic cardiomyopathy, dilated cardiomyopathy, or infiltrative disease (amyloid, Anderson-Fabry's disease), can present with chest pain syndromes. Over the past 2 decades, substantial knowledge has been gained on the use of CMR as a diagnostic test to further specify the underlying etiology of non-ischemic cardiomyopathies.[18]

The presence of dysfunction, edema, and the LGE pattern point toward the etiology of acute myocardial injury. However, in a subgroup of patients with acute chest pain and abnormal hsTn, no structural abnormalities were identified on CMR. In these cases, it is unclear whether this typically small hsTn elevation is due to myocardial injury or an alternate diagnosis. If assay-related analytical issues are excluded (e.g., heterophile antibodies, hemolysis, end-stage renal disease), alternative causes need to be considered.[12]

LGE can detect focal myocardial necrosis as small as 0.7 g or 0.4% of the LV mass.[19] Some patients can have very small areas of myonecrosis that are not detected with CMR. Alternatively, myocardial necrosis can be secondary to a diffuse process that is not visualized as regional change on imaging. Several examples of myocardial injuries with normal heart structure and tissue characterization on CMR are prolonged episodes of tachycardia, pulmonary embolism (often with right ventricular dysfunction), stroke (with and without ECG changes and/or LV dysfunction), strenuous exercise, and myositis (in particular, if hsTn assays are used).[20] However, troponin release in these situations might not represent true myocardial damage but rather release of cytosolic troponin or increased cell membrane permeability under stress.[12] In some clinical scenarios (e.g., motor vehicle accident with chest trauma and loss of consciousness or syncope during/after strenuous activity), CMR can be useful to exclude underlying structural heart disease as the cause for the inciting event and abnormal hsTn versus cardiac contusion and/or strenuous exercise alone.

A guidance statement from the European Society of Cardiology recommends early CMR for patients admitted to the hospital with MINOCA, namely those with positive cardiac biomarkers, corroborative evidence of infarction by symptoms, ST-T changes on ECG, and non-obstructive coronary arteries on angiography.[8] High-sensitivity assays increase detection of abnormal troponins in the ED, with subsequent normal or near-normal ICAs. Therefore, it is conceivable that CMR can be useful upfront to characterize the nature of myocardial injury, particularly when corroborative evidence of infarction (ST elevations) is inconclusive upon initial evaluation. **Figure 1** depicts one possible pathway to use of CMR (versus the traditional pathway) with routine admission and coronary angiography in all patients with abnormal hsTn.

In patients with an unstable clinical course due to life-threatening diseases such as pulmonary embolism, acute aortic dissection, hypotension or shock, sepsis, or acute respiratory distress syndrome, there is no need to evaluate an abnormal hsTn test further. Specific therapy should be initiated with emergent imaging, such as bedside echocardiography or computed tomography (CT) scan, as needed. However, in patients

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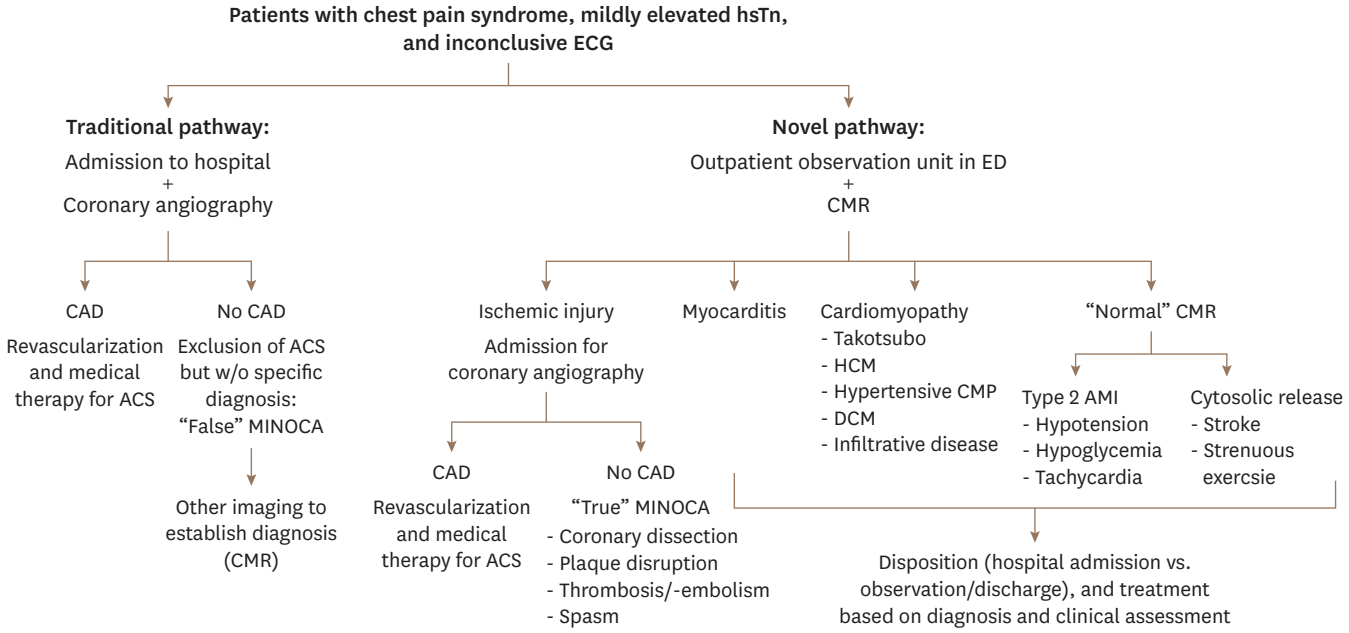

Figure 1. Management algorithm for patients with chest pain, mildly elevated high-sensitivity troponin, and inconclusive ECG. The left side of the algorithm shows a traditional management pathway that uses invasive coronary angiography to assess significant coronary disease. If the findings suggest type 1 myocardial infarction, appropriate therapies are administered. However, with insignificant coronary disease, ACS is excluded without a specific diagnosis ("False" MINOCA). Other imaging tests are needed to identify the process leading to myocardial injury but are inconsistently performed. A novel management pathway for patients presenting to the emergency department with chest pain, mildly elevated high-sensitivity troponin, and inconclusive ECG findings is shown on the right side of the algorithm. Noninvasive imaging with CMR can determine the etiology of myocardial injury. A broad range of structural heart diseases and/or cardiomyopathies can identify and guide further management and disposition. Even if the pre-test probability of these patients is low, ischemic injury can be present, and invasive angiography is needed to identify and treat ACS or "True MINOCA" (when nonsignificant CAD is found). The absence of structural heart disease suggests a type 2 AMI event or myocardial injury unrelated to ischemia.
ECG: electrocardiogram, MINOCA: myocardial infarction with non-obstructive coronary arteries, ACS: acute coronary syndrome, CMR: cardiac magnetic resonance imaging, AMI: acute myocardial infarction, CAD: coronary artery disease, HCM: hypertrophic cardiomyopathy, DCM: dilated cardiomyopathy, CMP: cardiomyopathy.

with stable clinical presentations, CMR can be useful to identify structural heart disease and provide diagnostic information on the underlying problem. It also can help to exclude acute cardiac disease and ACS, and aide in decision-making regarding disposition (hospital admission versus discharge) and specific therapies.

NOVEL MANAGEMENT ALGORITHMS FOR PATIENTS WITH ABNORMAL TROPONINS

Patients diagnosed with non-ST elevation acute coronary syndrome (NSTE-ACS) based on symptoms, ischemic ECG changes, and abnormal troponin level are typically admitted to an intermediate or step-down care unit and managed based on risk. This management will either include early invasive diagnostics and potential revascularization or an ischemia-guided strategy with non-invasive testing.[21] An early invasive therapy is superior to an ischemia-guided strategy for those with definite ACS and high risk features such as refractory or recurrent angina, hemodynamic instability, ventricular arrhythmias, new or dynamic ischemic ECG changes, or high risk scores (GRACE[22] or TIMI[23]). In contrast, an imaging-guided strategy can avoid costly and possibly unnecessary invasive procedures in those with low-risk ACS, those with comorbidities, or those with particular patient/physician preferences. Abnormal troponin level is commonly used as an indicator of higher-risk ACS. According to the current American College of Cardiology (ACC)/American Heart Association

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guidelines for NSTE-ACS, non-invasive stress testing should be performed in low- to intermediate-risk patients who are symptom-free for at least 12 to 24 hours (unstable angina) or for 2 days (NSTEMI).[21]

With use of hsTn, there is a significant shift in ACS patients from unstable angina ("normal" troponin) to NSTEMI (detection of "abnormal" troponins). In theory, these guidelines would identify more patients at higher risk and lead to more invasive coronary angiographies performed early and/or longer hospital admissions for imaging studies. However, use of hsTn has led to the assertion that many patients with mildly abnormal hsTn without ischemic ECG changes have acute CNCDs or type 2 AMI, rather than type 1 AMI.[3] Therefore, new strategies to manage acute chest pain patients are needed, such as that depicted in **Figure 1**. In these new algorithms, non-invasive testing with CMR or other modalities such as cardiac CT (obtained while patients remain in outpatient observation units) act as pivotal gatekeepers for hospital admission and invasive angiography.

SAFETY CONSIDERATION OF CMR IN THE ED

One concern regarding use of CMR is that it will delay important therapies in patients who have an equivocal evaluation for ACS (and might have type 1 ACS). The use of early stress testing in this patient population can lead to adverse events. Notably, the most recent consensus statement on the appropriate use criteria (AUC) of imaging in the ED in patients with suspected NSTE-ACS states that imaging at rest without stress physiology (most typically with single-photon emission computed tomography [SPECT] or cardiac CT) is appropriate. The consensus statement states that echocardiography or CMR might be appropriate to assess regional wall motion abnormalities in those with an equivocal initial diagnosis of ACS. For those undergoing observation (with serial ECGs and troponins) and either negative or borderline ACS stress/rest echocardiography, CMR, SPECT/positron emission tomography, and cardiac CT are considered appropriate. Interestingly, for patients who are unequivocally positive for NSTEMI/ACS, stress imaging "may be appropriate" but there was a lack of consensus among panelists. Regarding timing, the AUC authors state that patients can undergo imaging 9 to 24 hours after ED presentation (as long as it is safe and not clinically contraindicated) with no recommendation regarding optimal timing. Furthermore, no distinction is made between stress modality of those that elicit ischemia (dobutamine or exercise) versus those that use vasodilators (adenosine, regadenoson, dipyridamole).[24]

In this context, adenosine has been studied extensively as a cardioprotective agent in AMI in clinical trials and was shown to reduce infarct size.[25] In these protocols, adenosine was administered as an intravenous infusion to patients with ST-elevation AMI in higher doses than those used for diagnostic imaging. The adenosine was initiated prior to revascularization in these protocols. Although adenosine can theoretically be detrimental in AMI due to coronary steal, brady-arrhythmias, and negative inotropic effects, the AMISTAD trial showed a relatively low associated rate of bradycardia, hypotension, or atrioventricular (AV) block, even with a 3-hour intravenous infusion protocol.[25] For stress CMR, adenosine is typically administered over 3 minutes and has been shown to have an excellent safety profile and ultrashort half-life (< 10 seconds) in a wide range of patients with known or suspected CAD.[26]

Finally, the ACC clinical guidelines for exercise stress testing from 2002 endorse a class IIa recommendation for exercise testing in intermediate-risk unstable angina patients defined as

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those with troponin T > 0.01 but < 0.1 mg/mL, which represents an 8-fold order of magnitude higher than that of the currently available hsTn essays (0.1 mg/mL = 100,000,000 ng/L).[27] Therefore, it appears that the perceived risk of stress testing in patients with abnormal troponin reflects the pre-high-sensitivity assay era, with fewer subjects having abnormal troponins. In the current era, many of the abnormal hsTn tests, even in those with ACS, would have been within normal limits on older generation troponin assays. Therefore, these patients would have been deemed low risk.

REVIEW OF THE LITERATURE ON CMR IN ED PATIENTS

Search criteria

A detailed literature search was completed on the use of CMR in patients presenting to the ED with chest pain or findings concerning for ACS. The search was completed in the PubMed database using pertinent Medical Subject Headings (MeSH) terms: "Emergency Service, Hospital," "Non-ST Elevated Myocardial Infarction," "Magnetic Resonance Imaging," and "Troponin." The resulting articles were further filtered by inclusion of certain MeSH terms in the title or abstract. Only studies published in English and involving human subjects were considered. The search yielded 111 studies. All of the abstracts were reviewed, yielding 31 relevant articles that underwent further evaluation. The pertinent review articles on CMR in the ED or in patients with chest pain were reviewed in detail. The relevant citations from these publications were explored. We only included studies that looked at patients presenting to the ED with chest pain or elevated troponins. CMR had to be performed in the ED, in a clinical observation unit if such a unit existed, or in a timely manner following admission from the ED. Case reports and review articles were excluded. Further, studies that looked at the use of CMR in outpatients with stable angina or patients who had had a recent negative invasive coronary angiogram were excluded. A detailed methodology summary is available in **Appendix 1**. Ultimately, 8 articles were selected (**Table 1**).

Overview of the included studies

A total of 8 studies investigating the use of CMR in the ED and published between 2003 and 2019 were included.[28-35] These 8 studies included a total of 676 patients (range 29 to 161) who presented with acute chest pain at centers with expertise in CMR in the US (5), Germany (1), the Netherlands (1), and the United Kingdom (1). There were 2 randomized clinical trials, comparing CMR versus routine care in patients with NSTEMI[34] and those with no definite evidence of ACS and normal troponin essays.[32] Five studies were prospective cohort analyses, and one was a retrospective study. In 4 studies, patients with elevated troponins were included.[30][33-35] Four studies only enrolled patients with normal troponins.[28][29][31][32] A high-sensitivity troponin assay was used in only one of the studies (Smulders). Of note, as previously discussed, because high-sensitivity troponin assays have only recently become widely used, it is conceivable that many of the troponin-negative patients in these studies might have had an abnormal high-sensitivity troponin level.

In all 8 studies, patients with ST-elevation MI were excluded. Furthermore, patients were excluded if they were too medically unstable to undergo CMR due to severe heart failure or ongoing ischemia; had contraindications to adenosine (high-grade AV block, severe bronchospastic disease); or had contraindications to MRI (implanted metal devices) or gadolinium-based contrast agents.

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Table 1. Summary of literature review articles on cardiac magnetic resonance imaging in patients presenting to the emergency department

Reference	Number	Tn (+ or –)	Study design	Aim	Inclusion criteria	Exclusion criteria	Endpoints	Main findings	CMR protocol (all = 1, select = 2, none = 0)					Scan time (minutes)
									Cine	LGE	Perfusion	MRA	T2W	
Heitner et al.[28]	60	–	Prospective cohort	To compare utility and efficacy of adenosine stress CMR to stress echocardiography in the ED setting in patients with acute chest pain, and intermediate risk	Chest pain, intermediate risk of CAD	i) Low risk: atypical chest pain without risk factors ii) High risk: ECG changes of infarct/ischemia or abnormal Tn iii) Known CAD iv) Severe aortic stenosis, 2nd or higher degree AV block, pregnancy, clinical instability v) Standard MRI contraindications	Composite of > 50% stenosis on ICA, new acute MI, death at F/U (14 ± 5 months)	Sensitivity 100%, specificity 92% to detect primary composite endpoint (8/60)	1	1	1 stress/ rest¶	0	0	< 50
Ingkanisorn Et al.[29]	135	–	Prospective cohort	Diagnostic & prognostic value of adenosine CMR to identify CAD and adverse events in chest pain patients in the ED	Chest pain, negative Tn, ECG not diagnostic of STEMI or ischemia	i) NYHA class IV CHF ii) 2nd or 3rd degree AV block iii) Hemodynamic instability iv) Asthma/bronchospastic disease v) Standard MRI contraindications	Composite of > 50% stenosis on ICA, SPECT confirming abnormal CMR findings, new acute MI, death at 1 year	Sensitivity 100%, specificity 91% to detect primary composite endpoint (20/135)	1	1	1 stress/ rest¶	0	0	Not specified
Kwong et al.[30]	161	+ or –	Prospective cohort	Detection of ACS in ED patients with chest pain	Chest pain (≥ 30 min duration) within 12 hours before ED presentation, age > 21 years, weight < 270 lbs.	i) STEMI ii) Pregnancy iii) Severe CHF iv) MRI contraindications	Diagnostic accuracy for detection of ACS	Sensitivity 84%, specificity 85% for detection of ACS (25/161)	1	1	1 (rest)	0	0	38 ± 12
Lerakis et al.[31]	103	–	Retrospective cohort	To evaluate the negative predictive value of adenosine stress CMR in low-risk acute chest pain patients	No persistent ischemic-type chest pain, negative Tn-I, normal or inconclusive ECG	i) Standard MRI contraindications ii) Adenosine contraindications iii) Pulmonary embolism iv) Acute neurological disease v) Suspicion for acute aortic syndrome vi) NYHA class IV CHF	Composite of cardiac death, nonfatal acute MI, hospitalization for unstable angina, or > 50% stenosis on ICA at F/U (9; 5–15 months)	Negative predictive value 100% for primary endpoint	1	1	1 stress/ rest¶	0	1	45
Miller et al.[32]	105 (52 CMR)	–§	RCT	Effect of stress CMR in ED/COU vs routine care on revascularization, hospital readmission, and recurrent testing at 90 days	Chest pain, without definite evidence for ACS, intermediate risk (TIMI risk ≥ 2), age > 21 years	i) Definite ACS ii) Known inducible ischemia iii) Hypotension iv) CMR contraindications v) Life expectancy < 3 months vi) Pregnancy vii) PCI/CABG within 6 months viii) Increased risk for nephrogenic systemic fibrosis	Primary: composite of revascularization, readmission, recurrent testing at 90 days Secondary: i) LOS ii) Safety composite of death, adverse events of stress testing, or ACS at 90 days	i) Reduction in primary endpoints w CMR: 7 (13%) vs. 20 (38%) in usual care ii) Hospital admission avoided in 85% w normal CMR iii) Safety: ACS after discharge in 3 (6%) of usual care patients vs. 0 in CMR group iv) LOS shorter (21 hours CMR group vs. 26 hours usual care)	1	1	1 stress/ rest‖	0	1	58 (53–65)

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Table 1. (Continued) Summary of literature review articles on cardiac magnetic resonance imaging in patients presenting to the emergency department

Reference	Number	Tn (+ or –)	Study design	Aim	Inclusion criteria	Exclusion criteria	Endpoints	Main findings	CMR protocol (all = 1, select = 2, none = 0)					Scan time (minutes)
									Cine	LGE	Perfusion	MRA	T2W	
Plein et al.[33]	68	+	Prospective cohort	Diagnostic accuracy for the detection of significant CAD on ICA in NSTEMI	NSTEMI with chest pain, rise in the serum Tn-I levels, and/or ischemic changes on ECG for patients listed for ICA	i) Overt clinical heart failure ii) MRI or adenosine contraindications	CAD ≥ 70% on ICA	Sensitivity 96%, specificity 83% to detect CAD on ICA (56/68)	1	1	1 stress/rest¶	1	1	62.5 ± 7.7
Smulders et al.[34]	207 (68 CMR)	+	RCT	Whether CMR or CTA can reduce referral to ICA without detrimental effect on clinical outcome in patients with NSTEMI vs. routine care	Chest pain, normal/inconclusive ECG, elevated hs-cTnT	i) Ongoing severe ischemia requiring immediate ICA ii) Chest pain of non-MI origin iii) Type II MI iv) Age > 85 years v) Contraindications for CMR & CTA	Primary: proportion of patients referred to ICA Secondary: safety by absence of MACE (death, MI, unplanned revascularization, CHF hospitalization) or procedure-related complications at 90 days and 1 year	i) Reduction in primary endpoint with 87% (CMR), 66% (CTA) vs. 100% in routine care ii) Similar rate of MACE and procedure related complications with 19% (CMR), 15% (CTA) vs. 23% in routine care	1	1	1 stress/rest†,¶	0‡	1	Not specified
Steen et al.[35]	29	+	Prospective cohort	Feasibility/value of CMR for diagnosis in chest pain unit	Chest pain with elevated TnT, non-conclusive symptoms, and normal/non-diagnostic ECG with low-intermediate probability of CAD	i) High likelihood for ACS ii) Asymptomatic patients with ESRD and constant level of TnT	Feasibility of CMR in chest pain unit	i) CMR performed in 29 patients without complications; in 7 CMR could not be performed due to claustrophobia or metal implant ii) Diagnosis made in 27/29 patients	1	2*	1 (rest)	Pulmonary	2	35 ± 8

ACS: acute coronary syndrome, AV: atrioventricular, CABG: coronary artery bypass grafting, CAD: coronary artery disease, COU: clinical observation unit, CHF: congestive heart failure, CTA: computed tomography angiography, CMR: cardiac magnetic resonance imaging, ECG: electrocardiogram, ED: emergency department, ESRD: end stage renal disease, F/U: follow up, hs-cTnT: high-sensitivity cardiac troponin T, ICA: invasive coronary angiography, lbs: pounds, LGE: late gadolinium enhancement, LOS: length of stay, MACE: major adverse cardiac events, MI: myocardial infarction, MRA: magnetic resonance angiography, MRI: magnetic resonance imaging, NSTEMI: non-ST elevation myocardial infarction, NYHA: New York Heart Association, PCI: percutaneous coronary intervention, RCT: randomized controlled trial, SPECT: single-photon emission computerized tomography, STEMI: ST elevation myocardial infarction, T2W: T2-weighted, TIMI: thrombolysis in myocardial infarction score, Tn: troponin, TnT: troponin T.

*Unless aortic dissection; †Adenosine perfusion planned at end of protocol when diagnosis still unknown; ‡Transversal, multiplane bright-blood images for anatomy and extracardiac pathology; §Troponin was positive in 3 patients, who underwent stress CMR without adverse events during test or at 90 days post discharge; ‖Adenosine, regadenoson, or dobutamine as alternative; ¶Adenosine.

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In most of the studies, CMR was performed while the patient was in the ED. However, some centers in Europe admit patients to a dedicated chest pain unit, reflecting health care organizational variation.[33-35]

Study aims

The studies varied with regard to aims and primary endpoints. The majority of the studies (5 of the 8 studies) was designed to assess the accuracy of CMR or various imaging components to detect ACS, defined either by the presence of significant stenosis on ICA and/or by adverse cardiac events after discharge from the ED. One study by Lerakis et al.[31] specifically evaluated the negative predictive value of normal adenosine stress CMR in low-risk acute chest pain patients. Whereas many of these investigations focused on the diagnosis of CAD, Steen et al.[35] evaluated the feasibility, safety, and clinical value of CMR for diagnosis of non-coronary causes of elevated troponin in patients with non-conclusive symptoms and ECG.

Finally, 2 studies compared novel management strategies of CMR versus routine care in patients presenting to the ED with chest pain. Smulders et al.[34] examined whether cardiac MRI and CTA can reduce referrals to invasive cardiac catheterization without a detrimental effect on clinical outcomes in patients with clinical diagnosis of NSTEMI. Notably, the investigators excluded patients with clinically suspected non-coronary diseases associated with myocardial injury (myocarditis, pulmonary embolism) or type 2 AMI (tachycardia, severe hypertension, or severe aortic valve stenosis). The primary efficacy endpoint was proportion of patients referred for cardiac catheterization, with secondary safety endpoints of occurrence of major adverse cardiac events (MACE) and procedure-related complications within 1 month and 1 year.[34] Similarly, Miller et al.[32] compared the effects of CMR versus standard of care on clinical outcomes with the primary composite endpoint of revascularization, readmission, and recurrent testing at 90 days in patients with chest pain but no definite evidence of ACS.

CMR study results

The published studies demonstrated the feasibility of using CMR in ED patients with chest pain, with inability to perform CMR in 4% to 19% of patients, mostly due to body size, metal implants, or claustrophobia.[28][29][33-35] The 8 studies, which included nearly 700 patients, demonstrated the safety of CMR. More than half of the total patients underwent vasodilator stress perfusion imaging, and 5 studies included patients with abnormal troponin results. There were no serious adverse events related to the CMR procedure. Ingkanisorn et al.[29] described that the adenosine infusion was terminated prematurely in 4 patients because of associated symptoms, but they were able to obtain perfusion images. One test was terminated because the patient experienced a panic attack after perfusion imaging, but there were no clinical sequelae. Plein et al.[33] reported that perfusion imaging was not completed in one subject because of dyspnea and chest tightness with adenosine. The reported intolerances are consistent in severity and frequency to prior reports of vasodilator stress imaging.[26]

The pre-test probability for CAD varied significantly between studies, which was determined mostly by whether or not those with abnormal troponins were included. Therefore, the disease prevalence ranged from as low as 12% in one study that excluded individuals with abnormal troponins[32] to as high as 82% in another study that enrolled patients with abnormal troponins and ischemic ECG changes.[33] The diagnostic performance of CMR to detect CAD was high, with a sensitivity ranging from 84% to 100% and specificity from 83% to 92%.

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Steen et al.[35] investigated the broader use of cardiac MRI to evaluate potential non-coronary etiologies of myocardial injury in patients with abnormal troponins and a low suspicion for ACS based on lack of typical angina, low-intermediate probability of CAD, and a normal or nondiagnostic ECG. A specific diagnosis of acute non-coronary disease was made in 93% of patients, including myocarditis (17%), takotsubo cardiomyopathy (7%), infiltrative disease (3%), and pulmonary embolism (21%). Despite a low suspicion for ACS on clinical assessment, 40% of patients had MRI findings suggestive of ACS. The remainder of the studies was normal or suggestive of Tn elevation in the setting of renal disease.

Two studies randomized patients into novel, CMR-guided pathways in the ED or traditional management strategies that frequently include hospital admission and ICA. In the more recent 2019 CARMENTA trial, Smulders et al.[34] randomized 207 patients with acute chest pain, abnormal hsTn, and inconclusive ECG. The study compared a CMR- or CTA-first strategy with a control strategy of routine clinical care. Both the CMR- and CTA-first strategies reduced ICA compared with routine clinical care (87% [p = 0.001], 66% [p < 0.001], and 100%, respectively), which was the primary study endpoint. Patient safety, as defined by the absence of MACE (death, MI, unplanned revascularization, heart failure hospitalization) and procedure-related complications at 1 year, occurred in 23% of patients in the routine clinical arm and 19% of patients in the CMR-first strategy (p = 0.56). The authors concluded that a novel strategy implementing CMR or CTA first in the diagnostic workup in NSTEMI is a safe decision tool. In a second trial, Miller et al.[32] randomized 105 intermediate-risk patients with symptoms of ACS but without definite ACS based on the first ECG and troponin assay results to usual care or observation in a chest pain unit with stress CMR. The primary composite endpoints of coronary artery revascularization, hospital readmission, and recurrent cardiac testing at 90 days occurred in 20 (38%) usual care patients and 7 (13%) CMR-first patients (hazard ratio 3.4; p = 0.006). The median length of stay was shorter in the CMR-first strategy. Safety, defined as ACS after discharge, was favorable for CMR, with 3 patients having ACS in the usual care arm and 0 in the CMR-first arm.

CMR protocol

The CMR protocols include a number of core components such as cine imaging, LGE, and perfusion with and without adenosine vasodilator stress. T2-weighted sequences for assessment of myocardial edema were frequently performed. Some centers also performed morphological images. Plein et al.[33] evaluated the use of coronary MRA and found it to be a useful component. However, the time needed to acquire the typically 3-dimensional data set must be weighed against the incremental value over the core components. The scan time was typically less than one hour and ranged from an average of 35 minutes to 62.5 minutes.

DISCUSSION

There is a limited number of studies investigating the use of CMR in patients presenting with chest pain to the ED. Regardless, these studies have demonstrated several important findings. First, it is feasible and safe to use CMR with vasodilator stress perfusion in ED patients, including even those with abnormal troponins. No serious adverse events have been reported. Some studies have implemented a staged imaging protocol, whereby stress perfusion was performed only if no other imaging finding of ACS, (such as regional wall motion abnormalities or edema) was noted. An example of a CMR imaging protocol with techniques and typical findings in ED patients implemented in our lab is shown in **Figure 2**.

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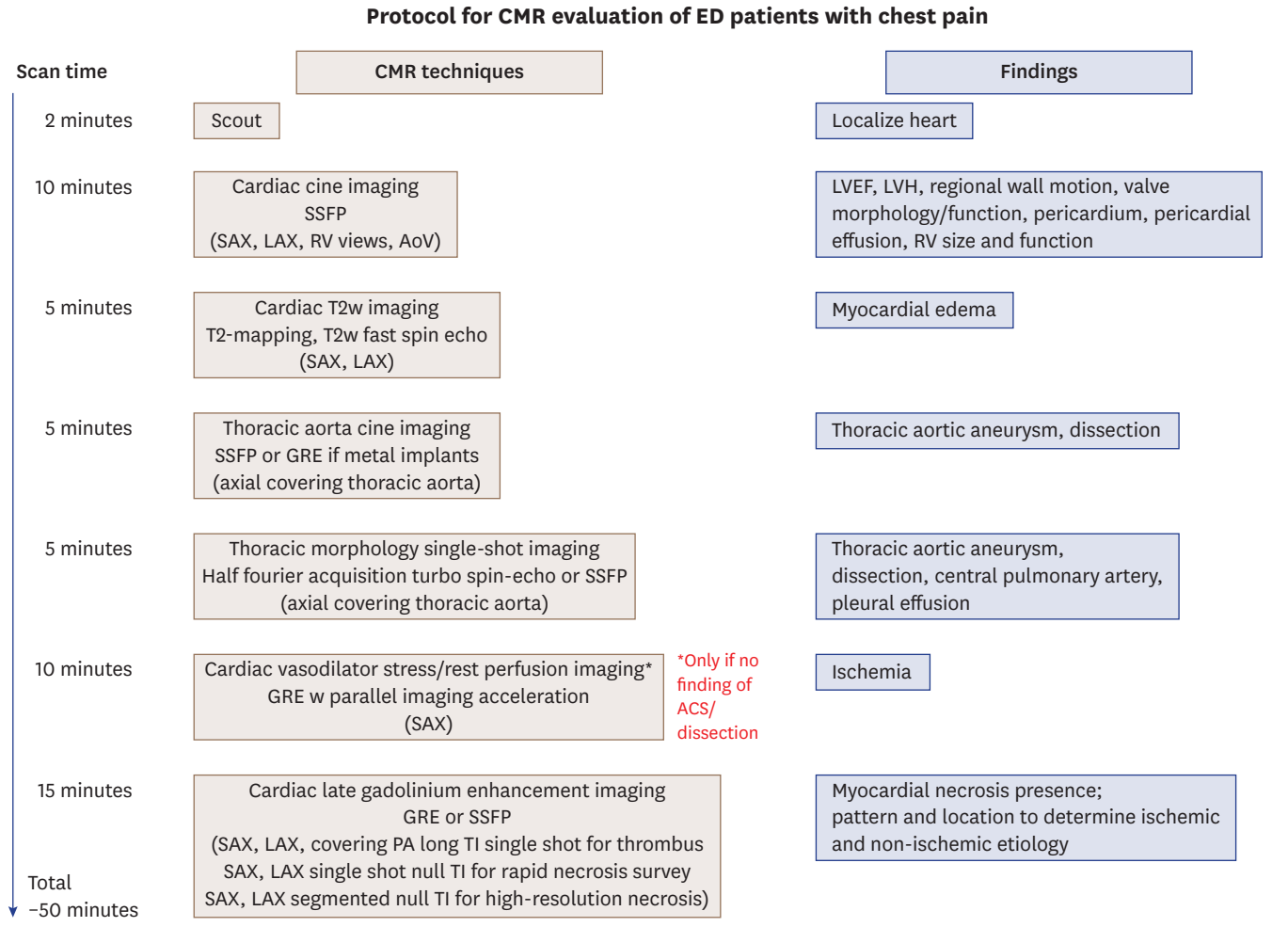

Figure 2. CMR protocol for evaluation of ED patients with chest pain. An example of a CMR protocol is shown and can be used to determine the etiology of chest pain and abnormal troponins in patients presenting to the ED.
CMR: cardiac magnetic resonance imaging, ED: emergency department, SSFP: steady state with free precession, SAX: short axis, LAX: long axis, RV: right ventricular, AoV: aortic valve, LVEF: left ventricular ejection fraction, LVH: left ventricular hypertrophy, GRE: gradient-recalled echo, PA: pulmonary artery, ACS: acute coronary syndrome.

We proceed in a stepwise fashion to adenosine perfusion if no acute aortic pathology or ACS is identified. The entire study is completed in less than one hour.

It remains unclear whether it is safe to perform vasodilator stress imaging after a patient presents to the ED or after onset of chest pain. The recommendations are based, in part, on concepts from studies investigating pre-discharge exercise testing in an era when medical treatment was limited (e.g., quinidine, propranolol, and digoxin) and hospitalizations for an AMI were typically 2 weeks long.[36] Nonetheless, with regard to timing, the guidelines state that patients can undergo imaging 9 to 24 hours after ED presentation (assuming that it is safe and not clinically contraindicated). Patients should be free from ischemia at rest or with a low-level of activity for a minimum of 12 to 24 hours prior to stress testing.[24] Furthermore, the risk associated with 2 to 3 minutes of vasodilators, such as adenosine or regadenoson, can be different from that of symptom-limiting exercise or dobutamine administration.

Second, the use of CMR is particularly useful for identifying the correct diagnosis in patients who present with chest pain, with or without abnormal hsTn, and in whom the

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initial evaluation of symptoms, risk factors, and ECG has not confirmed a diagnosis. Two patient examples are provided in **Figure 3**. As shown by Steen et al.[35] several CNCDs can be diagnosed with CMR. Notably, some patients with non-diagnostic clinical and ECG findings can have ACS detected by CMR. Therefore, a systematic clinical assessment approach can help to determine a patient's probability of having ACS. For example, the History, ECG, Age, Risk Factors, and Troponin (HEART) score has been shown to accurately predict MACE in ED patients.[37] Algorithms in which low-to-intermediate-risk patients with mildly abnormal hsTn could be triaged in an outpatient clinical observation unit with CMR would be useful to reduce hospital admissions while improving diagnosis and management in this patient group.

Third, from an economic perspective, outpatient evaluation can be more effective than routine admission with ICA in patients without a clear diagnosis after the initial clinical assessment. Both Smulders and Miller have shown that a CMR-first strategy can help to safely avoid or shorten admissions without increased rates of ACS, MI, death, revascularization, or CHF complications.[32][34]

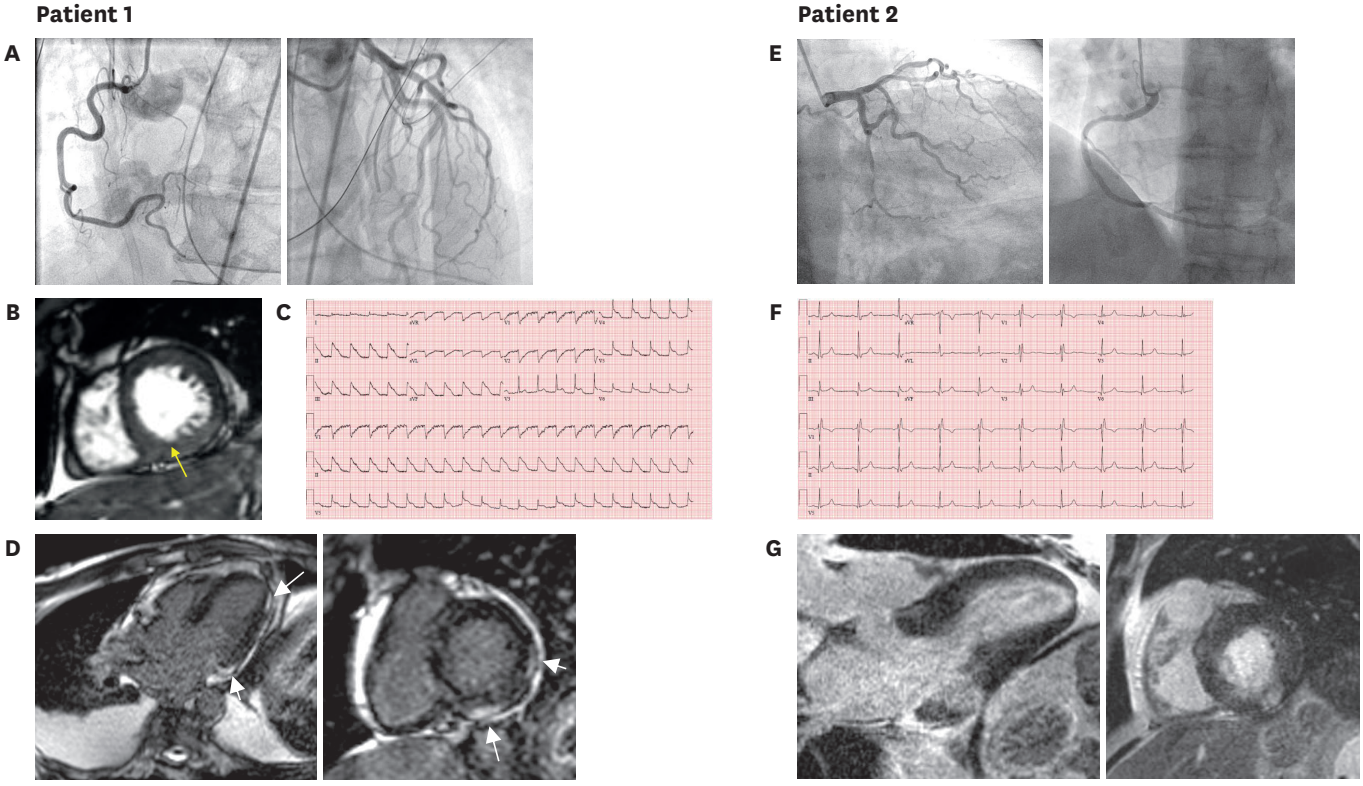

Figure 3. Patient examples demonstrating utility of CMR in chest pain patients. (A-D) Patient 1 is a 52-year-old male with past medical history of type 2 diabetes mellitus and COVID-19 infection who was brought in by ambulance with fever 100.8° F, hypotension with systolic blood pressures in the 80s mmHg, and hypoglycemia. He was found to have elevated lactate, elevated white blood cell count, and acute renal failure requiring intubation and vasopressors. On day 2 of hospitalization, ECG demonstrated new ST-segment elevation in the inferior and inferolateral leads (C). X-ray coronary angiography showed minimal, non-obstructive coronary artery disease, and he was diagnosed with MINOCA (A). CMR revealed myocardial edema (B, yellow arrow) and epicardial enhancement (D, white arrow) suggestive of myocarditis (e.g., no ischemic injury) and, therefore, "False MINOCA." (E-G) Patient 2 is a 42-year-old female with a past medical history of hypertension who presented with chest pain and an elevated white blood cell count. An ECG showed no ST or T changes (F). High-sensitivity troponins (hsTn) showed a baseline of 232 ng/L, 1-hour hsTn of 249 ng/L, and 3-hour hsTn of 257 ng/L indicating myocardial injury. The patient was admitted to the hospital and underwent X-ray coronary angiography, which showed a 60% small obtuse marginal 2 lesion and a 20% proximal right coronary artery lesion. She was diagnosed with MINOCA, and no intervention was performed (E). CMR was performed to further evaluate for myocarditis and showed a focal, transmural myocardial infarct in the basal inferolateral wall suggesting a "True MINOCA" (G).
CMR: cardiac magnetic resonance imaging, COVID-19: coronavirus disease 2019, MINOCA: myocardial infarction with non-obstructive coronary arteries.

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CONCLUSION

CMR is a feasible, safe, and economically effective alternative to traditional management in patients presenting to the ED with chest pain and an unclear diagnosis. It is a practical and non-invasive tool to risk-stratify patients in whom there is concern for cardiac pathology but inconclusive initial studies.

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Appendix 1

Literature search methodology

The search was completed using 3 main parts. The first part aimed to focus on articles about cardiac magnetic resonance imaging (MRI) with or without stress cardiac magnetic resonance imaging (CMR). This was done using the following query: "(Magnetic resonance imaging"[Mesh]OR "magnetic resonance"[tiab] OR MRI[tiab]) AND (cardiac[tiab] OR cardiovascular[tiab] OR heart[tiab] OR myocardial[tiab] OR coronary[tiab]) OR cMR[tiab] OR cMRI[tiab] OR ((cardiac[tiab] OR heart[tiab] OR stress[tiab]) AND magnetic[tiab] imaging[tiab]. The second part helped to focus on patients presenting to the emergency room with chest pain or found to have an non-ST elevation myocardial infarction (NSTEMI). The following query was used: "Emergency Service, Hospital"[Mesh]OR "emergency room"[tiab] OR "emergency rooms"[tiab] OR "emergency department"[tiab] OR "emergency departments"[tiab] OR "Non-ST Elevated Myocardial Infarction"[Mesh]OR NSTEMI[tiab] OR "Non–ST-Segment ElevationMyocardial Infarction" OR "chest pain"[tiab]. Finally, to ensure selection of articles focused on acute chest pain, and ideally those with positive troponins, the third part used the following simpler query: "Troponin"[Mesh]OR troponin[tiab] OR troponins[tiab].

A PubMed search was completed using the three parts above with "AND" logic, i.e. 1 AND 2 AND 3, with exclusion of case reports. Only patients published in English and involving human subjects were considered. The search yielded 111 relevant papers.

Abstracts were reviewed for all 111 papers by 1 author, yielding 31 relevant articles worth further evaluation. 80 were excluded either due to lack of relevance or case reports which were not filtered by the original query. Pertinent review articles on CMR in the ED or in patients with chest pain were reviewed, and relevant citations from those publications were explored. 57 articles underwent secondary review by 2 authors to determine which were appropriate for inclusion. Ultimately, 8 articles were selected for inclusion meeting the following inclusion and exclusion criteria:

- Inclusion criteria: Randomized controlled trial or cohort analysis looking at the use of cardiac MRI in patients presenting to the emergency department with chest pain or elevated troponins. Cardiac MRI had to performed in the emergency department, in a clinical observation unit if such a unit existed in that hospital, or immediately following admission from the emergency department.

- Exclusion criteria: Case reports. Review articles. Studies looking at the use of CMR in outpatients with stable angina or patients who had had a recent negative invasive coronary angiogram.

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