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Magnetic resonance imaging for diagnostic workup of embolic stroke of undetermined source: A systematic review

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Abstract

Background: Embolic stroke of undetermined source (ESUS) refers to ischemic stroke where the underlying cause of thromboembolism cannot be found despite the recommended diagnostic workup. Unidentified source of emboli hinders clinical decision-making and patient management with detrimental consequences on long-term prognosis. The rapid development and versatility of magnetic resonance imaging (MRI) make it an appealing addition to the diagnostic routine of patients with ESUS for the assessment of potential vascular and cardiac embolic sources.

Aims: To review the use of MRI in the identification of cardiac and vascular embolic sources in ESUS and to assess the reclassification value of MRI examinations added to the conventional workup of ESUS.

Summary of review: We reviewed the use of cardiac and vascular MRI for the identification of a variety of embolic sources associated with ESUS, including atrial cardiomyopathy, left ventricular pathologies, and supracervical atherosclerosis in carotid and intracranial arteries and in distal thoracic aorta. The additional reclassification after MRI examinations added to the workup of patients with ESUS ranged from 6.1% to 82.3% and varied depending on the combination of imaging modalities.

Conclusion: MRI techniques allow us to identify additional cardiac and vascular embolic sources and may further decrease the prevalence of patients with the diagnosis of ESUS.

Keywords

MRI, CMR, ESUS, reclassification value

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Introduction

Embolic stroke of undetermined source: a diagnostic challenge

Embolism to the cerebral arteries is the most important mechanism of ischemic stroke, accounting for most acute cerebrovascular events.[1] Correct identification of the underlying etiology is a complex undertaking, and in as many as 30% of all strokes, the thromboembolic source remains unknown despite extensive diagnostic workup. This situation has traditionally been described as cryptogenic stroke (CS), which was approached as a diagnosis of exclusion, although no standardized diagnostic criteria existed for CS. Since 2014, these strokes are classified as embolic stroke of undetermined source (ESUS) in an effort to standardize disease nomenclature and facilitate clinical research.[2,3] The recommended diagnostic workup in ESUS includes brain CT or brain magnetic resonance imaging (MRI), 12-lead electrocardiogram (ECG), continuous ECG monitoring (⩾24 h), precordial echocardiography, and imaging of extracranial and intracranial arteries supplying the infarct area.[3] However, despite this comprehensive workup, the underlying embolic source remains undetermined in nearly one out of four patients, with major implications for management and secondary prevention.[4]

ESUS remains a poorly defined group that cannot be treated as a single entity according to the results of recent trials.[5] Identifying the potential etiology is therefore crucial for the optimization of secondary prevention in this recurrence-prone group.[2] MRI can accurately diagnose a large variety of ESUS-linked conditions and constitutes appealing complementary imaging modality in ESUS, owing to its non-invasive nature, absence of radiation exposure, and excellent soft-tissue contrast. Herein, we examine the role of MRI in the identification of cardiovascular embolic sources in ESUS and evaluate its incremental diagnostic potential in this challenging clinical scenario.

Methods

This review study was registered in PROSPERO (CRD42020190504) and is reported according to the Synthesis without meta-analysis in systematic reviews (SWiM) and Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Reporting Guidelines, where applicable. Two independent researchers performed a systematic review of the MEDLINE and the Cochrane Library for relevant articles in humans published from the inception date to November 2022 (Figure 1). Available evidence on the characteristics of ESUS patients and the incremental diagnostic value of MRI techniques was pooled and summarized in graphical format. Details of search strategy, eligibility criteria, data extraction, quality assessment, and certainty of evidence are provided in the Supplemental Material.

Results

Atrial cardiomyopathy

Six articles were analyzed, including a total of 1143 patients. Out of 930 patients for whom gender was available, 370 (39.8%) were females.

Two studies reported a greater extent of atrial fibrosis, seen as late gadolinium enhancement (LGE) on cardiac MRI (CMR), in patients with ESUS compared with healthy controls. The extent of atrial LGE in patients with ESUS was comparable with patients with atrial fibrillation (AF) in three studies.[6–8] Atrial LGE was comparable between patients with ESUS and with known causes of stroke.[9] Two articles reported improved predictive performance of CHA2DS2-VASc score when combined with atrial fibrosis.[10,11] A total of 12% atrial LGE threshold identified patients at a higher risk of ESUS.[6,7]

Left ventricular embolic sources

Seven articles were analyzed, including a total of 1826 patients. Out of 1714 patients for whom gender was available, 480 were female (28.0%).

CMR accurately differentiated 6 cardiac tumors from 16 thrombi with a significantly different signal intensity ratio on delayed enhancement CMR.[12] For patients with CMR-identified thrombi, the incidence of stroke was significantly higher compared with controls.[13] LGE consistent with previous myocardial infarction was found in 14.6% of ESUS patients.[14] Unrecognized myocardial infarction was associated with ESUS[15] and was an independent predictor of future adverse cardiovascular events in patients with ESUS.[16]

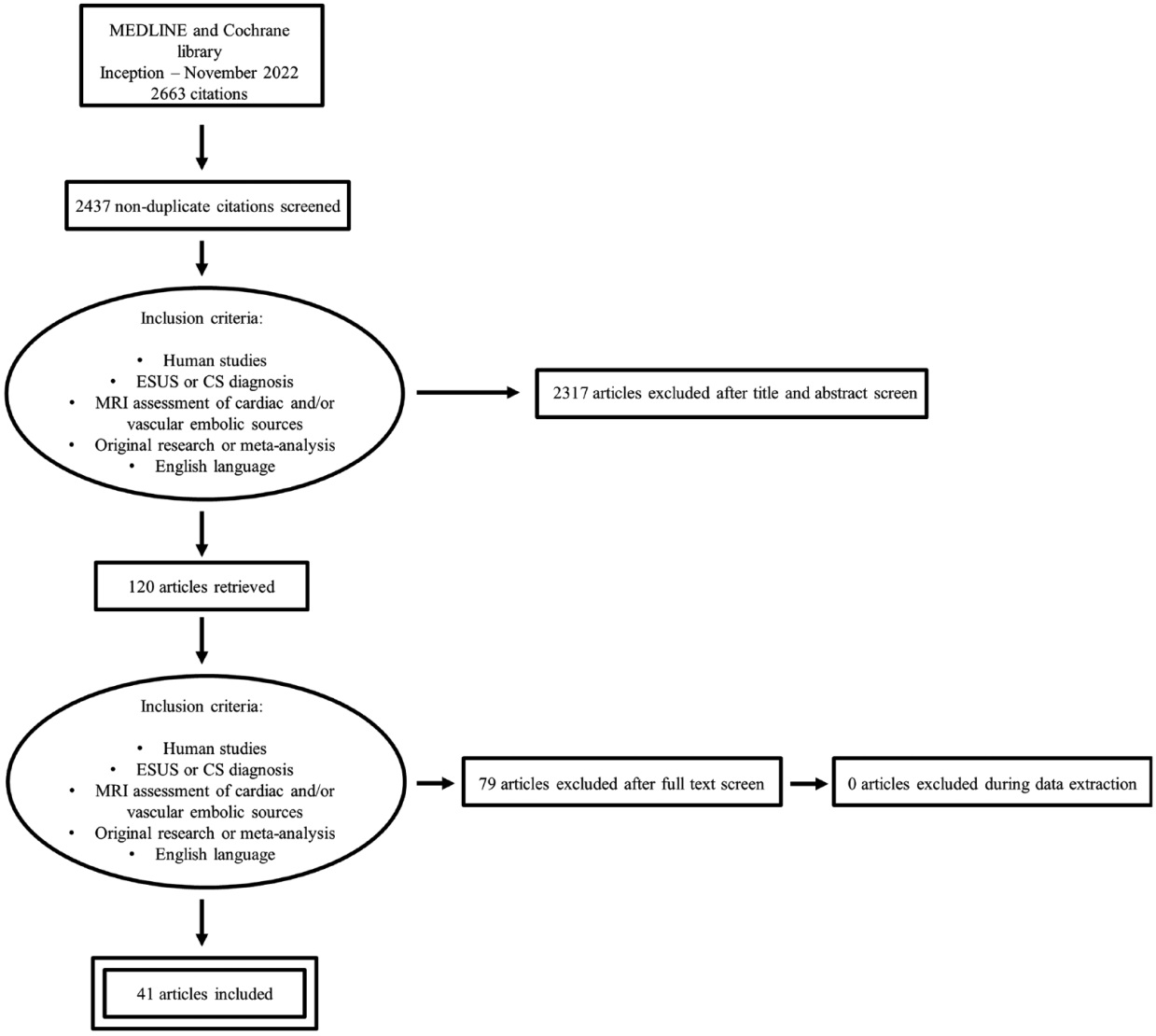
CMR identified cardiomyopathy in 6 out of 70 (8.57%) patients with ESUS, including four patients with hypertrophic cardiomyopathy and two patients with restrictive cardiomyopathy.[17] Non-compacted left ventricular (LV) mass and non-compacted-to-compacted LV mass ratio were significantly greater in ESUS patients compared with controls, although no participants satisfied the criteria for non-compaction cardiomyopathy.[18] In another study, high-risk embolic sources identified on CMR in patients with ESUS included one case of Takotsubo cardiomyopathy.[14]

Carotid atherosclerosis

Eight studies were analyzed, including a total of 582 patients. Out of 353 patients for whom gender was available, 114 were female (32.3%).

Seven studies reported a higher prevalence of ipsilateral high-risk AHA lesion type VI plaques compared with contralateral plaques.[19–25] There was a higher prevalence of intraplaque hemorrhage (IPH) in ipsilateral plaques[19,24,25] and in plaques with a lower degree of stenosis.[26] In

Figure 1. The PRISMA flow diagram.



CS: cryptogenic stroke; ESUS: embolic stroke of undetermined source; MRI: magnetic resonance imaging.

particular, mildly stenotic carotid arteries in patients with ESUS had higher IPH compared with moderate and severe stenosis.[26]

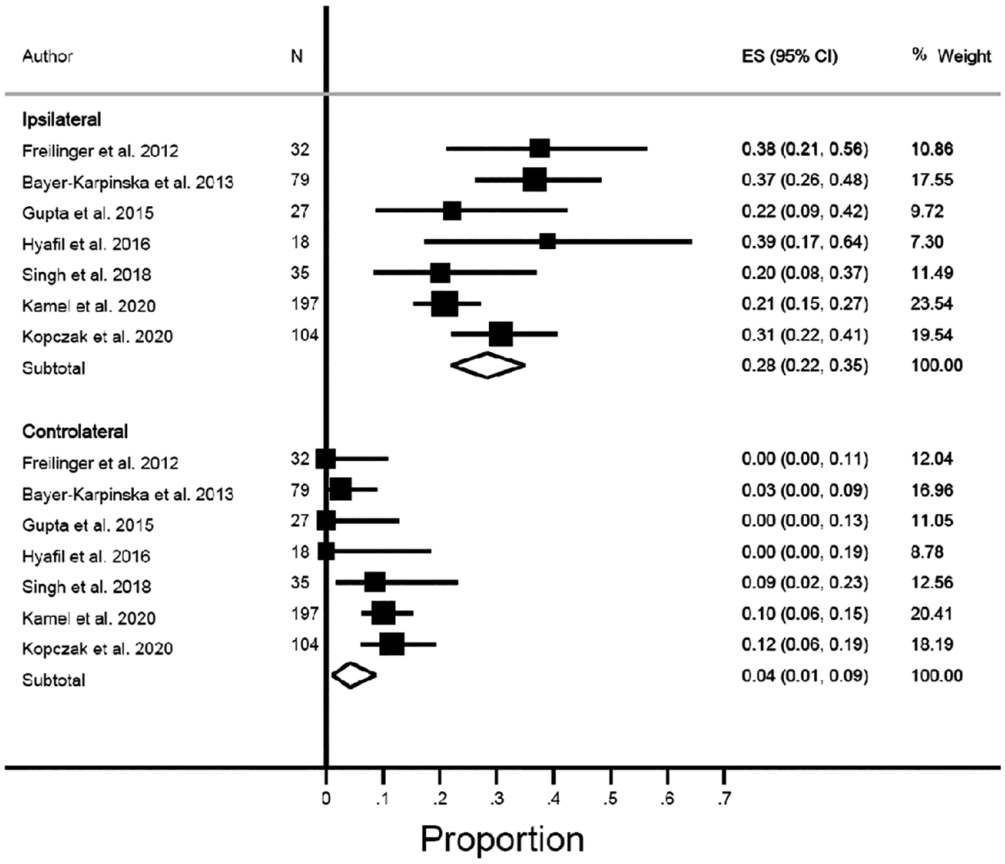
The pooled prevalence of ipsilateral high-risk carotid plaques across seven studies was 28% compared with 4% for contralateral plaques (Figure 2).

Intracranial atherosclerosis

Seven studies were analyzed, including a total of 813 patients. Out of 537 patients for whom gender was available, 190 were female (36.5%).

Vessel-wall MRI (VW-MRI) identified intracranial plaques in patients with ESUS with otherwise normal MRI angiography[27] and allowed a significant increase in intracranial atherosclerotic disease detection in ischemic stroke.[28] Ipsilateral intracranial plaques were more common than contralateral plaques among ESUS patients.[29] Remodeling index was independently associated with ESUS in two studies.[29,30] In a 7T VW-MRI study, contrast enhancement ratio $\geqslant 53$ ($p=0.008$), stenosis $\geqslant 50\%$ ($p<0.001$), and concentric morphology ($p=0.030$) were independent predictors of culprit plaques.[31] Non-stenotic plaque location, remodeling index, plaque burden,

Figure 2. Pooled prevalence of non-stenosing high-risk AHA-LT VI plaques in patients with ESUS.



discontinuity of plaque surface, presence of complicated plaques, and IPH differed significantly between cortical ESUS, subcortical ESUS, and mixed ESUS groups.[32] In a small study, 75% of COVID-19 patients with ESUS had concentric intracranial vessel wall enhancement consistent with inflammation.[33]

Aortic arch atherosclerosis

Eight studies were analyzed, including a total of 301 patients. Among 143 patients for whom gender was available, 66 were female (46.1%).

All studies demonstrated the presence of high-risk aortic plaques in patients with ESUS, with prevalence ranging from 17.5% to 63%.[34–40] MRI was more accurate in detecting aortic high-risk plaques compared with transesophageal echocardiography (TEE).[38,41] Vulnerable plaques ≥ 4 mm were more frequent in patients with ESUS than in controls[34] and in stroke patients compared with controls.[35] Four studies identified potential embolization pathways via retrograde diastolic blood flow.[34,35,37,40] The frequency of plaques with potential embolization pathway was comparable between patients with ESUS and patients with known stroke etiology in two studies.[35,36] Aortic pulse wave velocity (PWV) was higher in ESUS patients than in controls.[39]

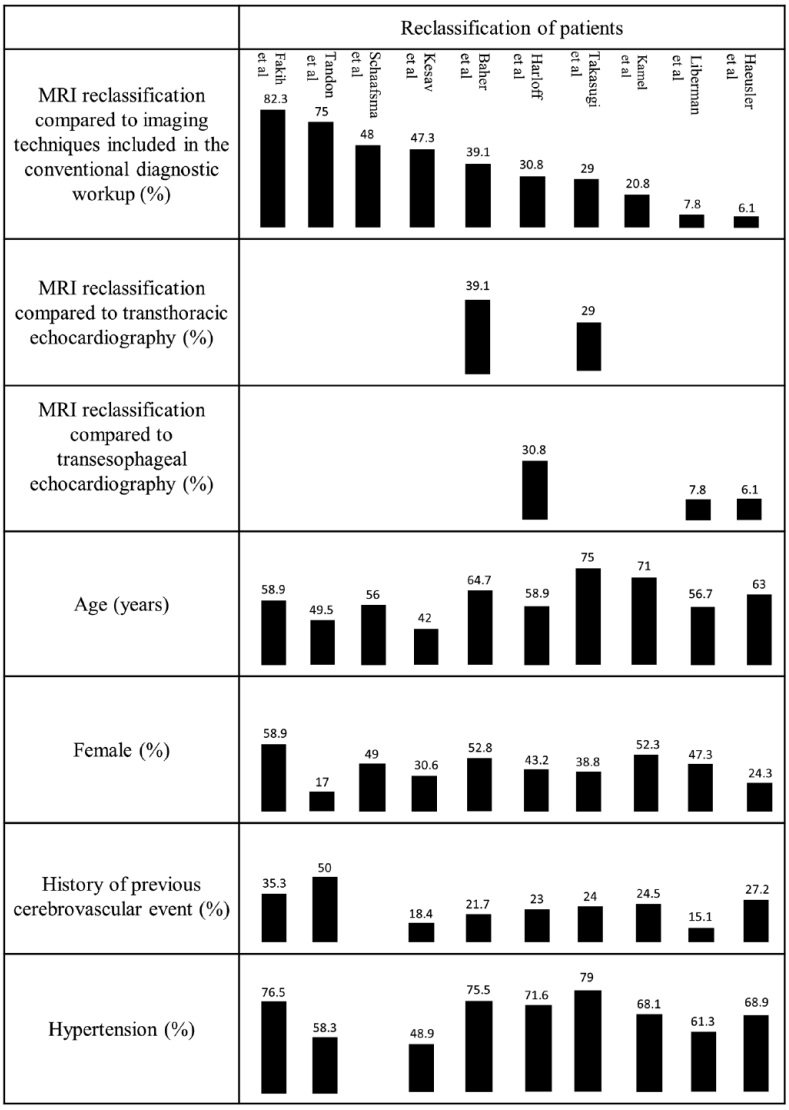
Reclassification potential of MRI techniques in ESUS

Ten studies were analyzed, including a total of 2080 patients, 911 (43.8%) of whom were females.

A total of 39.1%[42] and 29%[43] of patients with ESUS were reclassified into other stroke categories based on the CMR performed after standard ESUS workup with transthoracic echocardiography (TTE). A total of 6.1%[14] and 7.8%[44] of patients with ESUS were reclassified based on CMR results after TEE. A total of 20.8% and 30.8% of patients with ESUS were reclassified after carotid MRI and MRI of the aorta, respectively.[24,38]

VW-MRI performed after standard ESUS workup allowed to reclassify 47.3%[45] and 48%[28] of patients with ESUS. In the presence of suspicious findings in the middle cerebral artery on luminal imaging, VW-MRI reclassified 75%[46] of patients with ESUS. In a 7T MRI study of patients with ESUS with suspicious findings on luminal imaging, 82.3% of patients were reclassified.[31]

Figure 3. Harvest plot: MRI reclassification potential in patients with ESUS. Each black bar is annotated with a number depicting relevant patients' demographic characteristics and the percentage of patients in each study reclassified by MRI as compared with conventional imaging modalities in the diagnostic workup of ESUS.



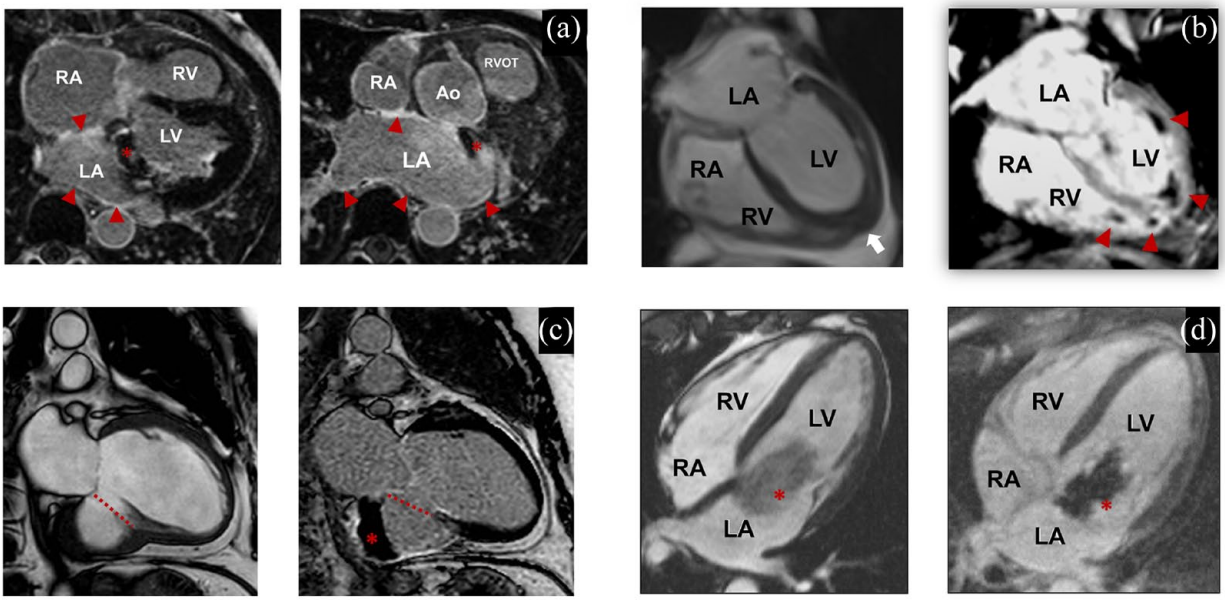
The reclassification potential of MRI techniques along with the characteristics of patients with ESUS is summarized in Figure 3.

Discussion

Identification of the embolic source remains a major challenge in the management and secondary prevention of stroke patients. ESUS diagnostic domain represents a large and heterogeneous group of stroke patients for whom a definitive embolic source cannot be identified after the standardized diagnostic workup. We reviewed the literature to assess the role of MRI in identification of embolic sources in ESUS, with a focus on atrial cardiomyopathy, LV embolic sources, and supracardiac atherosclerosis.

Atrial cardiomyopathy represents a potential contributor to the pool of ESUS etiologies easily overlooked by conventional workup. Atrial cardiomyopathy encompasses structural, contractile, and electrophysiological abnormalities of the atria, which can develop before AF onset and promote AF through structural and functional atrial remodeling. In turn, long-standing AF induces further atrial fibrosis in a self-sustained bidirectional process with an increased risk of systemic thromboembolism with or without detectable arrhythmia.[47] CMR contributes valuable complementary imaging findings to the

Figure 4. Cardiac pathologies in ESUS patients, not discovered with standard workup. (a) A 57-year-old female patient with mechanic prosthetic valve (*), presenting with ESUS. LGE imaging shows extensive fibrosis of the posterior LA wall, interatrial septum, and the origin of the right pulmonary vein (red arrowheads). (b) A 53-year-old woman with multiple ischemic strokes and increased peripheral eosinophil count. Cine image (left) showed an apparently hypertrophied LV apex (white arrow). Early post-contrast image (right) showed multiple LV and RV thrombi (red arrowheads). The clinical and imaging features were in keeping with Loeffler myocarditis. (c) A 55-year-old male patient with a history of inferior infarction. The cine (left) and LGE (right) images show a large pseudoaneurysm with a broad connection to the LV chamber (red dashed line) and a large, stratified thrombus (*). (d) A 47-year-old woman with ESUS. The cine (left) and LGE (right) images show a heterogeneous, irregularly shaped mass (*) of the anterior mitral leaflet, consistent with myxoma.



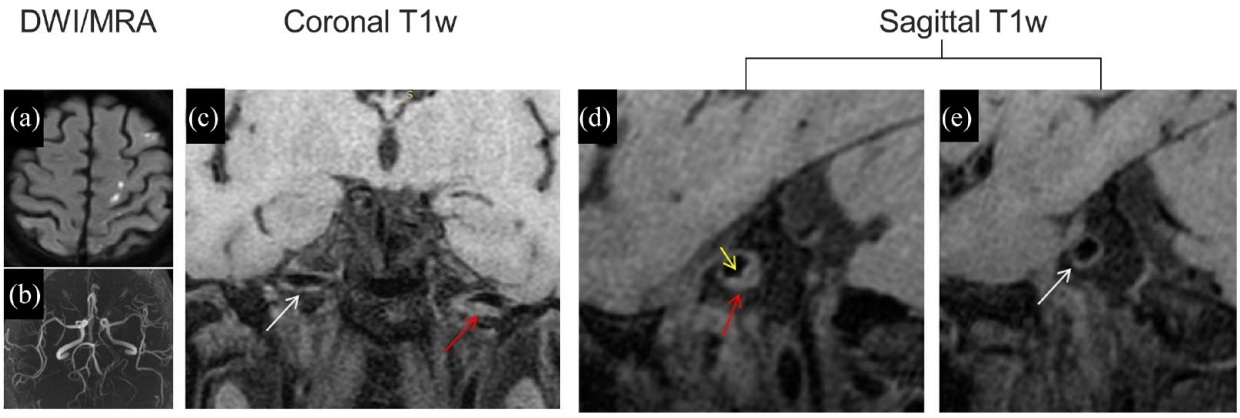
LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle; RVOT: right ventricular outflow tract; Ao: aortic root.

first-line left atrium assessment by TTE, including direct visualization of fibrotic burden, seen as hyperintense LGE areas on delayed enhancement images (Figure 4(a)). In the reviewed studies, the atrial fibrotic burden was associated with increased odds of stroke in patients with known AF[10] and outperformed the CHA_2DS_2-VASc score for the prediction of LA thrombosis.[10,11] Atrial LGE in patients with ESUS was significantly greater than in controls[6,9] and was comparable with AF patients,[8,9] suggesting the widespread presence of pro-arrhythmic and thrombogenic substrates among the former. A total of 12% atrial LGE threshold was proposed to identify patients at a higher risk of ESUS, independently of the presence of FA,[6,7] which could establish fibrotic burden as a potential decision-making tool.[47] A recently published protocol for a prospective multicenter CARM-AF study will aim to identify patients with ESUS at risk of future thromboembolism due to atrial cardiomyopathy through non-invasive CMR and ECG data.[48]

The unparalleled soft-tissue contrast and robust temporal resolution of CMR allow reliable detection and characterization of a variety of LV embolic sources (Figure 4(b) to (d)). CMR can accurately detect LV thrombi, which appear markedly hypointense on early and delayed enhancement images,[49] and reliably differentiate them from tumors and other cardiac masses (Figure 4(d)).[12] CMR also allowed to identify LV pathologies associated with thrombus formation and increased risk of embolic stroke,[14] including cardiomyopathies, where altered cardiac morphology and hemodynamic changes promote pro-thrombogenic environment (Figure 4(b)),[50] and previously undiagnosed myocardial infarction characterized by subendocardial or transmural distribution of hyperintense LGE on delayed enhancement CMR (Figure 4(c)).[15]

The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification required an atherosclerotic plaque causing a ⩾50% stenosis in a large brain-supplying artery for the definition of large-artery atherosclerotic stroke.[51] However, it becomes increasingly apparent that the assessment of atherosclerotic plaques in ESUS should include a broader set of plaque characteristics associated with substantial embolic risk.[52] In-depth tissue characterization by MRI allows to identify a variety of high-risk plaque features classified as AHA-LT VI plaques, including fibrous cap rupture, lipid-rich necrotic core, intraluminal thrombus, and IPH (Figure 5).[53]

Figure 5. A complicated non-stenotic carotid petrous plaque in ESUS. The petrous site is a transition segment between extracranial and intracranial carotid artery with increased predisposition to non-stenotic atherosclerotic changes. Diffusion-weighted imaging (a) demonstrates left cortical infarct in the internal carotid artery territory, without significant stenoses on MRI angiography (b). Coronal (c) and sagittal (d and e) T1-weighted MRI demonstrate a vulnerable plaque (red arrow) of the ipsilateral petrous segment, with fibrous cap rupture (yellow arrow), compared with a smaller stable contralateral plaque (white arrow).



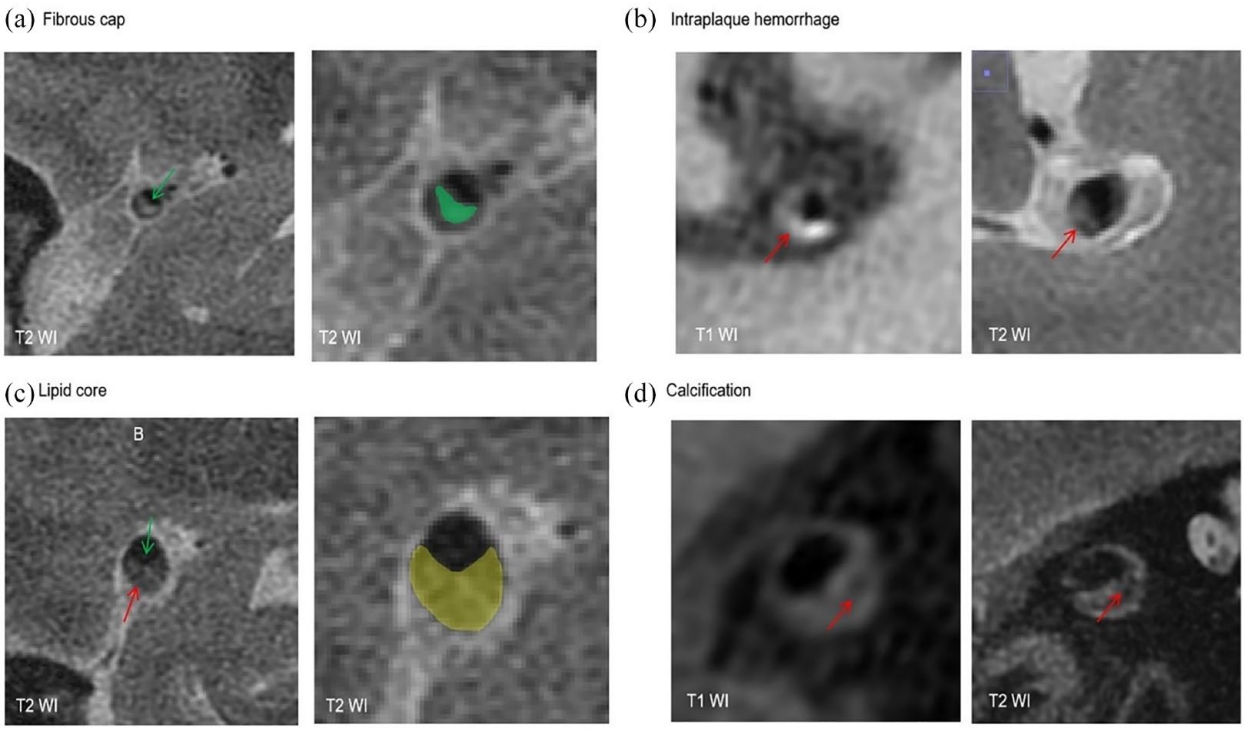
All included studies demonstrated a higher prevalence of ipsilateral carotid AHA-LT VI plaques in ESUS patients compared with the contralateral side, which is consistent with a recent meta-analysis.[54] The pooled prevalence of ipsilateral high-risk carotid plaques was 28% versus 4% for contralateral plaques, an imbalance that suggests a causative association between ESUS and ipsilateral non-stenotic high-risk plaques. Higher prevalence of T1-hyperintense IPH in ipsilateral plaques, especially in the setting of mild stenosis, might be indicative of its role in embolism from non-stenotic carotid plaques.[26]

MRI also allows in-depth assessment of intracranial atherosclerotic plaques, which can be present in up to 16% of patients with ESUS.[55] High-resolution VW-MRI allows us to go beyond the evaluation of the vascular lumen and assesses a variety of distinct intrinsic MRI characteristics of non-stenotic intracranial plaques[29] (Figure 6). A recently published meta-analysis showed an association between symptomatic plaques and VW-MRI features of contrast enhancement and intrinsic T1-hyperintensity, which is thought to represent IPH.[56] Concentric intracranial vessel wall enhancement consistent with inflammatory changes was identified on VW-MRI assessment in COVID-19 patients with ESUS.[33] Ipsilateral plaques were also more likely to present positive remodeling and have complicated morphology.[29] Remodeling index (vessel area at the maximal luminal narrowing divided by reference vessel area) was associated with ESUS in two studies and is an expression of an adaptive mechanism aimed to preserve the vascular lumen by bulging in the presence of atherosclerotic plaques.[29,30]

Aortic arch atherosclerosis (AAA) can be found in as many as 29% of patients with ESUS.[57] While TEE readily identifies complex plaques in the proximal aorta,[58] it has limited utility for plaques in the distal arch and descending aorta. Moreover, TEE cannot visualize end-diastolic retrograde blood flow, which creates potential embolization pathways by transporting plaque material backward to the brain-supplying arteries. Advanced MRI techniques such as 4D flow reliably visualize high-risk distal aortic plaques, as well as their potential embolization pathways.[34,35,37,40] Complex distal AAA plaques and retrograde embolization pathways were comparable between patients with ESUS and patients with known stroke etiology,[34] suggesting a possible causative link between ESUS and AAA. Aortic PWV, which is a marker of aortic stiffness and precursor AAA lesions, was associated with reverse flow from descending aorta plaques in patients with ESUS, but not in controls, further stressing the role of AAA in ESUS etiology.[39]

Although a variety of ESUS-linked conditions can be reliably identified on MRI, relatively little is known about the overall reclassification value of adding MRI examinations to ESUS workup and whether it translates into significant changes in patient management. Moreover, reclassification rates range from as little as 6.1% to 82.3%. This notable gap can be partially attributed to the combination and characteristics of imaging modalities used in the workup of patients with ESUS prior to MRI examination (Table 1). Considerable reclassification rates of 29–39.1% in CMR examination after standard ESUS workup with TTE[42,43] highlight the well-documented limitations faced by TTE, including acoustic windows, operator dependency, and limited sensitivity for some potential embolic sources. In comparison, lower reclassification rates were reported for CMR performed in addition to TEE,[14,44] suggesting limited benefit in performing both TEE and CMR in the same

Figure 6. Plaque characteristics of intracranial atherosclerotic lesions on histology-verified VW-MRI. (a) An intracranial plaque characterized by a thick fibrous cap, seen as a hyperintense band on T2w (green). (b) An intracranial plaque featured by a large lipid core content, seen as hypo- to isointense T2 signal (red, yellow outline), covered by a thin fibrous cap seen as hypointense band on T2w (green). (c) An intracranial plaque with intraplaque hemorrhage, hyperintense on fat-suppressed T1w (red). (d) An intracranial plaque containing calcifications, seen as hypointense signals on T1w and T2w (red).



T1w: T1-weighted imaging; T2w: T2-weighted imaging.

Table 1. Reclassification potential of MRI techniques among ESUS and CS patients.

Study	Number of patients	ESUS or CS patients (%)	Compared with	Reclassified patients (%)
Liberman et al.[44]	93	68.80	TEE	5/64 (7.80)
Baher et al.[42]	106	27.10	TTE	9/23 (39.10)
Haeusler et al.[14]	103	79.6	TEE	5/82 (6.10)
Takasugi et al.[43]	797	22	TTE	4/14 (29)
Harloff et al.[38]	74	39.20	TEE	8/26 (30.80)
Kamel et al.[24]	579	34	Conventional imaging workup	41/197 (20.80)
Schaafsma et al.[28]	205	16.1	Conventional imaging workup	16/33 (48)
Kesav et al.[45]	49	38.8	Endoluminal vessel imaging (CTA, MRA, and/or DSA)	9/19 (47.3)

MRI: magnetic resonance imaging; ESUS: embolic stroke of undetermined source; CS: cryptogenic stroke; TEE: transesophageal echocardiography; TTE: transthoracic echocardiography; CTA: computed tomography angiography; MRA: magnetic resonance angiography; DSA: digital subtraction angiography.

patient. CMR is not equivalent to TEE in most clinical scenarios, although it might have some utility in selected high-risk subgroups or in patients who refuse or are unable to undergo TEE. High reclassification rate of ESUS patients after VW-MRI can be partially attributed to high pre-test probability due to preliminary assessment with luminal imaging.[28,31,45,46] The reclassification in this setting was even higher (82.3%) with a 7T MRI scanner,[31] accounting for its superior signal-to-noise ratio with higher spatial resolution and tissue contrast. However, the widespread implementation of 7T MRI in clinical settings is still in its developmental phase. MRI of the aorta reclassified nearly one-third of patients as ESUS due to improved visualization of the distal aorta compared with TEE, as described above.[38] MRI of the carotid arteries allowed reclassifying 20.8% of ESUS patients after accounting for ipsilateral high-risk plaques not detected on conventional ESUS workup.[24] Interestingly, the study utilized neck coils instead of dedicated carotid coils and selected IPH as an indicator of plaque vulnerability, which improved the generalizability of the findings, but might underestimate or misclassify other high-risk carotid plaque features.

Importantly, therapeutic implications of these MRI-based etiologic changes remain largely to be defined, even as the results of recent trials demonstrated that ESUS cannot be approached with a "one-fits-all" secondary prevention strategy.[5,59] Some MRI-identified etiologies can prompt well-established secondary prevention approaches. For example, in the study by Baher et al.,[42] 30% of reclassified ESUS patients were started on anticoagulation therapy after MRI identification of evident embolic sources (either intracardiac or complex ascending aorta thrombus). VW-MRI findings of symptomatic intracranial plaques can prompt dual antiplatelet therapy and differentiate intracranial atherosclerosis from other pathologies with distinctly different management.[33] However, other etiologies still require evidence-based research on the optimal management strategy before their impact on prevention and prognosis will become clear. The AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke (ARCADIA) trial, which until recently investigated the use of apixaban versus antiplatelet therapy in ESUS patients with atrial cardiomyopathy without known AF, was prematurely terminated as the primary outcome of stroke recurrence occurred in similar rates among both groups.[60] It remains unknown whether this result should be attributed to the validity of the hypothesis itself, to the high treatment cross-over in patients with AF detected during the trial, or to the specific definition of atrial cardiopathy used in the trial, which did not include CMR findings. Similarly, limited evidence is available on optimal management strategies for non-stenotic high-risk carotid atherosclerosis and AAA. Further studies on their role in ESUS and the correlation of MRI markers with clinical outcomes are needed to devise successful prevention strategies.

Clinical implications and future perspectives

While an increasing number of physicians acknowledge the diagnostic value of MRI in the ESUS setting, there is a degree of clinical inertia toward its implementation. Commonly quoted factors include availability of the MRI facilities and patients' inability to complete MRI examination due to acutely impaired comprehension and consciousness. This is especially relevant for CMR examinations that can take around 45 min to complete and require patient's collaboration for breath-holding. However, in the CaMRISS study, 86% of selected stroke patients without existing MRI contraindications were able to fully complete the CMR.[14] The development of robust free-breathing sequences further decreases the overall scanning time and overcomes compliance limitations.[61] MRI costs are considered another important barrier to its wider use, although advancements in MRI technology are expected to decrease the one-off and maintenance costs of equipment and further curb the cost–benefit curve. At present, evidence on the financial implications of adding MRI to ESUS workup can only be approximated and should be formally evaluated by cost-effectiveness studies, especially with the advent of novel MRI techniques that will likely broaden its use, such as 4D flow for improvement of stroke prediction[62] and quantitative susceptibility imaging for differentiating IPH from calcifications.[63] The integration of deep learning algorithms in MRI acquisition, image processing, and interpretation is expected to enhance its effectiveness, optimize scanning times, and improve image quality.[64]

Cardiac CT is another technique with emerging potential for identifying embolic sources missed on standard ESUS workup, most importantly intracardiac thrombi and complex aortic plaques.[65] CT offers a robust and non-invasive method for evaluating cardiovascular embolic sources, while the use of dual-energy CT, perfusion imaging, and artificial intelligence applications will allow a more detailed characterization of atherosclerotic plaques and cardiac tissues in the future. However, there is a lack of studies comparing the diagnostic yield of relevant findings between CT, MRI, and other imaging modalities in patients with ESUS. Moreover, it is important to consider the implications of ionizing radiation, iodinated contrast media, and risks versus potential benefits in every scenario where cardiac CT is used as an alternative to other imaging techniques.

Conclusion

MRI is increasingly employed in the clinical routine and diagnostic algorithm of patients with ESUS and has the potential to decrease the working diagnosis of ESUS by pinpointing the underlying stroke etiology. Owing to its versatility and unique properties for tissue characterization, MRI may identify potential cardiovascular embolic sources that would be untraceable with the conventional

diagnostic algorithm of ESUS. Dedicated MRI sequences capable of capturing high-risk functional features beyond anatomical imaging may further boost the clinical applicability of this technique in the stroke setting. Comparative studies against other imaging modalities are needed to demonstrate the cost-effectiveness of MRI in ESUS investigation.

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Supplemental material

Supplemental material for this article is available online.

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