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Impact of clinician training background and stroke location on bedside diagnostic accuracy in the acute vestibular syndrome –a meta-analysis

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Abstract

Objective—Acute dizziness/vertigo is usually due to benign inner-ear causes but is occasionally due to dangerous neurologic ones, particularly stroke. Because symptoms and signs overlap, misdiagnosis is frequent and overuse of neuroimaging is common. We assessed the accuracy of bedside findings to differentiate peripheral vestibular from central neurologic causes.

Methods—We performed a systematic search (MEDLINE, Embase) to identify studies reporting on diagnostic accuracy of physical examination in adults with acute, prolonged dizziness/vertigo

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AUTHOR CONTRIBUTIONS

AAT, JAE, KAR and DNT contributed to the conception and design of the study; AAT, DG, JAE, ZW, GM, JK, AST, DSZ and DNT contributed to the acquisition and analysis of data; AAT, ZW, JAE and DNT contributed to drafting the text or preparing the figures.

POTENTIAL CONFLICTS OF INTERESTS

Nothing to report.

("acute vestibular syndrome" [AVS]). Diagnostic test properties were calculated for findings. Results were stratified by examiner type and stroke location.

Results—We identified 6089 citations and included 14 articles representing 10 study cohorts (n=800). The "HINTS" (Head Impulse, Nystagmus, Test of Skew) eye movement battery had high sensitivity 95.3% (95% CI 92.5-98.1) and specificity 92.6% (88.6-96.5). Sensitivity was similar by examiner type (subspecialists 94.3% [88.2-100.0] vs. non-subspecialists 95.0% [91.2-98.9], p=0.55), but specificity was higher among subspecialists (97.6% [94.9-100.0] vs. 89.1% [83.0-95.2], p=0.007). HINTS sensitivity was lower in AICA than PICA strokes (84.0% [65.3-93.6] vs. 97.7% [93.3-99.2], p=0.014) but was "rescued" by the addition of bedside hearing tests (HINTS+). Severe (grade 3) gait/truncal instability had high specificity 99.2% (97.8-100.0) but low sensitivity 35.8% (5.2-66.5). Early MRI-DWI (within 24-48 hours) was falsely negative in 15% of strokes (sensitivity 85.1% [79.2-91.0]).

Interpretation—In AVS, HINTS examination by appropriately trained clinicians can differentiate peripheral from central causes and has higher diagnostic accuracy for stroke than MRI-DWI in the first 24-48 hours. These techniques should be disseminated to all clinicians evaluating dizziness/vertigo.

Keywords

Vertigo; dizziness; diagnostic accuracy; bedside examination; emergency department

INTRODUCTION

Dizziness (spatial disorientation) and vertigo (false motion) are common vestibular symptoms[1] seen in general and neurological practice.[2] Severely affected patients often seek acute care in the emergency department (ED), where these symptoms together comprise 2.1 to 4.4% of all visits.[3-6] Annually, there are ~4.4 million such visits to US EDs resulting in estimated healthcare costs of over $10 billion.[7] The differential diagnosis of acute dizziness and vertigo is broad, cutting across organ systems and specialties. The plurality of cases are due to inner ear disorders, but no one disease accounts for more than ~5-10% of all cases, increasing the risk for both inappropriate diagnostic testing and diagnostic errors.[3] This latter issue is crucial, since over 15% of all ED patients with these symptoms suffer from a dangerous underlying cause.[3] The most common dangerous cause is stroke, accounting for ~3-5% of cases.[8]

Clinical fear of missing a stroke is justified, given that most strokes presenting with dizziness or vertigo lack obvious neurologic symptoms or signs such as lateralizing weakness or difficulty speaking.[9] As a result, dizziness due to stroke has a clinical phenotype that overlaps substantially with that seen in less serious disorders, particularly the self-limited peripheral vestibular diseases. Thus, two of the most common inner ear disorders, benign paroxysmal positional vertigo (BPPV) and vestibular neuritis, can easily be mistaken for stroke and vice-versa.[10] Neuroimaging is often insufficient to address this differential diagnosis, as non-contrast computed tomography (CT) scans have very low sensitivity (7-16%) for acute ischemic strokes in dizziness and false-negative MRIs are surprisingly common.[11]

Fortunately, the evidence base for effective bedside differentiation of inner ear diseases from stroke in patients with acute dizziness and vertigo has grown substantially over time.[8, 12] Different clinical signs pointing to a central cause in patients with acute vestibular syndrome (AVS – defined as acute prolonged vertigo/dizziness accompanied by nausea/vomiting, gait imbalance, nystagmus and motion intolerance)[13] have been proposed, emphasizing the combined use of targeted neuro-otologic bedside examination techniques such as HINTS (Head Impulse test, Nystagmus exam, Test of Skew),[14] HINTS+ (which adds a bedside test of hearing),[15] and assessing for gait/truncal instability.[16] This systematic review and meta-analysis seeks to summarize this evidence with a focus on the impact of training background and stroke location on accuracy. We also seek to compare these more specific vestibular tests with more “routine” bedside (vascular risk profiles, general neurologic examination) and neuroimaging (CT, MRI) tests.

METHODS

Data sources and searches

We searched MEDLINE and Embase for articles in any language with terms representing the following three components: (1) vertigo/dizziness, (2) diagnostic accuracy of bedside examination techniques, and (3) acute vestibular syndrome. We also performed a manual search of reference lists from eligible articles and contacted corresponding authors where necessary. We limited our search to articles published since 1980, when neuroimaging for stroke first became routine. Our search was updated through May 17, 2022.

Study selection and quality assessment

Articles were selected by two independent screeners using pre-determined inclusion criteria and a structured process. Our focus was on high level-of-evidence (LOE 1-3) studies (i.e., with an independent, blind comparison of signs and symptoms with a "gold standard" among consecutive or non-consecutive patients suspected of having the target condition) examining the diagnostic accuracy of clinical examination techniques for distinguishing between peripheral and central causes of AVS (i.e., symptom onset <72h) in unselected patient populations in the ED or on an acute inpatient ward. The requisite reference standard for “ruling out” stroke in a peripheral vestibular case was delayed magnetic resonance imaging with diffusion-weighted images (MRI-DWI); strokes could be “ruled in” using confirmatory neuroimaging, including computed tomography (CT) in the appropriate clinical context, but an unconfirmed clinical diagnosis was insufficient. Studies with low LOE-ratings were excluded. Subsequently, we assessed the risk of bias and applicability concerns for all studies selected using QUADAS-2 criteria. Full study details of selected studies are provided in supplementary Table 1.

Data extraction, synthesis and analysis

We report the diagnostic accuracy of clinical examination techniques to distinguish peripheral from central causes of AVS (ABCD2 vascular risk score, vestibular eye movement tests, gait/truncal stability, general neurologic examination). Prospectively defined subgroup analyses were performed, comparing diagnostic test properties (a) in the subgroup of patients with isolated central AVS (icAVS, i.e., absent obvious neurologic

signs, (b) stratified by specialty of the clinicians who performed the diagnostic maneuvers (subspecialists in neuro-otology or neuro-ophthalmology vs. non-subspecialists with other training backgrounds who were appropriately instructed in test performance), and (c) stratified by stroke vascular territory (posterior inferior cerebellar artery [PICA] vs. anterior cerebellar artery [AICA]).

We defined the following neurologic signs as “obvious”: facial palsy, hemisensory loss, crossed sensory loss, dysphagia, dysarthria, limb ataxia, mental status abnormality (e.g., lethargy), hemiparesis, ocular motor paralysis, Horner syndrome, or visual field loss. We defined the following neurologic signs as “subtle”: central eye movements without limited range of motion (e.g., central spontaneous or gaze-evoked nystagmus with central features [e.g., dominantly vertical or torsional in trajectory], ocular lateropulsion, saccadic smooth pursuit, dysmetric saccades, normal vestibulo-ocular reflexes), new hearing loss, or gait/truncal instability. The last was considered “subtle” because in the context of AVS, many peripheral vestibular patients have some degree of gait or truncal instability, so it does not uniformly point to a central lesion. Hearing loss was considered a “subtle” sign here as it often points to a peripheral lesion localization, however, counter to traditional teaching, the presence of such hearing loss more often indicates a vascular (labyrinthine or lateral pontine infarction) rather than a viral (labyrinthitis) cause of the AVS presentation.[15] These “subtle” signs were permitted in the icAVS subgroup.

We specifically included diagnostic accuracy for the composite HINTS and HINTS+ with test batteries. For HINTS “peripheral,” the patient needed to have all three features “peripheral” (i.e., Boolean “AND”)—a unilaterally abnormal hHIT with a direction-fixed, dominantly horizontal nystagmus beating contralaterally to the abnormal hHIT without a vertical skew deviation on alternate cover testing. Anything else was considered a “central” HINTS pattern (i.e., Boolean “OR” on any of the “central” findings—[a] bilaterally normal or bilaterally abnormal hHIT OR [b] direction-changing gaze-evoked nystagmus or unidirectional horizontal nystagmus beating towards the unilaterally abnormal hHIT or [c] presence of a vertical skew deviation on alternate cover testing). For HINTS+ “central” the hearing loss needed to be new, unilateral, and evident by bedside finger rub or similar testing.

A semiquantitative grading system (grade 0 to grade 3) was used to classify the extent of gait or truncal instability (GTI), with grade 0 indicating no GTI. Slightly diverging ratings for GTI grade 1 and 2 have been used in the literature. While one study defined grade 1 GTI as "mild to moderate imbalance with walking independently" and grade 2 GTI as "severe imbalance with standing, but cannot walk without support"[16], another study defined grade 1 GTI as "sway on Romberg" and grade 2 GTI as "able to stand but no tandem gait".[15] For grade 3 GTI, only minor differences in the definition amongst included studies were observed. While in one study this was referred to as "falling at upright posture"[16], others defined grade 3 GTI as inability to stand[17] or sit upright[15] unassisted.

We also calculated the diagnostic test properties of early MRI-DWI (within 48 hours of onset of AVS symptoms) with respect to final (delayed) MRI-DWI and compared these, where appropriate, to test properties for clinical history or examination. Finally, we extracted

data from a recent systematic review of CT and MRI neuroimaging in acute dizziness and vertigo to create comparative summary receiver operating characteristics (ROC) curves for both neuroimaging and bedside findings.[18]

We calculated sensitivity, specificity, negative likelihood ratio (LR−) and positive likelihood ratio (LR+) for ED or acute-ward diagnoses for any central condition (rather than stroke, per se, since the clinically relevant diagnostic branch point is differentiating central from peripheral disorders). We present proportions and, where appropriate, 95% confidence intervals (95% CI). Tests of heterogeneity were conducted based on Cochran's Q-test. For a study with zero cells, a continuity correction of 0.5 was added to all cells of that study (not to all studies). We also compared more recent (published 2016 or later) to older studies (published before 2016) to assess for differences in diagnostic accuracy or maldistribution of studies over time based on specialty. Summary ROC curves, summary points and confidence ellipses are estimated based on the bivariate model in Reitsma et al.[19] This model has been shown by Harbord et al.[20] to be equivalent to the hierarchical summary SROC model proposed by Rutter & Gatsonis.[21] Heterogeneity statistics (Cochran's Q-test) were calculated using R v4.2.1 (Foundation for statistical computing, Vienna, Austria) by a PhD biostatistician. This review is reported in accordance with PRISMA guidelines and the protocol was registered in PROSPERO (CRD42017050723).

Data availability

Source data used for meta-analysis will be made available to others upon request to the corresponding author.

RESULTS

Our search identified 6089 unique citations, of which 5508 (90.5%) were excluded at the abstract level (Figure 1 - PRISMA flow chart). We sought to examine 581 full manuscripts. At the end of our full-text review, 466 manuscripts were excluded and 115 were considered eligible, representing 1.9% of the total (n=6089).

Level of evidence and quality using QUADAS-2

A total of 33 studies (LOE1=12, LOE2=9, LOE3=12) were included, whereas 82 studies (LOE4=65, LOE5=17) were excluded based on low LOE. Higher LOE studies were then subjected to a complete quality assessment using the QUADAS-2 tool. Nineteen studies were rated as having high risk in one or more items and were also excluded.

Characteristics of studies and patients

Of the 14 included articles, four were preliminary reports from the same study cohorts and were thus not considered for the quantitative analysis. The proportion of central AVS (cAVS) cases was 52.8% (422/800). While ischemic stroke was the most common central cause (334/422, 79.1%), acute peripheral vestibulopathy (i.e., vestibular neuritis [without hearing loss, n=377] or labyrinthitis [with hearing loss, n=1]) was diagnosed in all patients with peripheral AVS (pAVS; n=377/378, 99.7%) (Table 1).

Five studies reported on icAVS-patients only,[16, 17, 22-24] whereas five studies included cAVS-patients with and without obvious neurologic signs.[15, 25-28] In those five studies that provided numbers on the distribution of cAVS-patients, icAVS-patients were more frequent than non-isolated cAVS-patients (66%, n=148/224) vs. (34%, n=76/224) ($p<0.001$). Among tests studied, elements of the HINTS battery were most frequently applied. Bedside testing was applied by experienced neuro-otologists or neuro-ophthalmologists with primary training in either neurology or otolaryngology (35.5% [n=284/800] patients),[15, 26, 27] general neurologists (13.4% [n=107/800] patients),[17, 24] trained neurology residents supervised by experienced neuro-otologists (14.3% [n=114/800] patients),[16] neurology residents (16.5% [n=132/800] patients),[28] and emergency physicians who had received 6 hours of training by "two expert otologists" on two separate occasions, separated by 7 months (11.0% [n=88/800] patients).[22]

Diagnostic accuracy of bedside examination findings

A summary receiver operating characteristic (SROC) curve shows the overall results plotting sensitivity and specificity for different bedside tests and providing neuroimaging accuracy point estimates for comparison and context (Figure 2). Individual test details are found in supplementary Table 2. Sensitivity for detecting a central cause of AVS was highest for a normal hHIT (79.9% [95% CI 72.2-87.5]), grade 2 or 3 gait/truncal instability (80.8% [45.1-100.0]) and saccadic vertical smooth-pursuit eye movements (84.3% [69.2-99.3]), but was considerably lower for the other tests including the test of skew (27.0% [16.1-37.9]), direction-changing nystagmus on lateral-gaze test (37.3% [27.2-47.3]) and spontaneous vertical or torsional nystagmus (23.1% [4.0-42.1]). Specificity for detecting a dangerous central cause of AVS was high for all these bedside tests.

Diagnostic accuracy of the HINTS composite-score for "ruling out" (sensitivity=95.3% [92.5-98.1]; LR−=0.09 [0.05-0.17]) and "ruling in" (specificity=92.6% [88.6-96.5]; LR+=7.95 [4.94-12.78]) cAVS causes was high in our meta-analysis (Figure 3). Adding a fourth test (new unilateral hearing loss), diagnostic accuracy of HINTS+ for "ruling out" (sensitivity=97.2% [94.0-100.0]; LR−=0.06 [0.02-0.21]) and "ruling in" (specificity=92.4% [86.9-97.9]; LR+=8.47 [3.66-19.56]) cAVS causes had the maximum accuracy of any bedside test combination from included studies.

Comparing the diagnostic likelihood ratio for different bedside tests in AVS (with post-test probability of stroke), HINTS and HINTS+[15] both outperformed other bedside tests (including the hHIT alone, gait/truncal instability assessment, and "obvious" neurologic findings) as well as neuroimaging by CT or MRI-DWI imaging in "ruling out" cAVS causes (Figure 2). In contrast, "ruling in" cAVS causes was similar amongst different bedside tests and imaging (Tables 2 and 3, Figure 3).

Heterogeneity in diagnostic accuracy for HINTS was statistically significant. Stratifying the diagnostic accuracy of HINTS by examiner specialty, SROC curves for subspecialists (Figure 4A) and non-subspecialists (Figure 4B) demonstrated higher specificity for the subspecialist group vs. the non-subspecialist group (97.6% [94.9-100.0] vs. 89.1% [83.0-95.2], p=0.007), whereas sensitivity values were very similar and not statistically different (94.3% [88.2-100.0] vs. 95.0% [91.2-98.9], p=0.55) (Figure 4 and supplementary

Table 3). Compared to either non-contrast CT-imaging or MRI-DWI, the diagnostic accuracy of HINTS was higher regardless of examiner group (Figure 4).

Diagnostic accuracy in AVS stratified by stroke location—The diagnostic accuracy in detecting cAVS causes was compared for two distinct stroke locations (PICA vs. AICA strokes) in Table 4. Whereas ruling out PICA strokes was excellent both when applying composite scores (HINTS, HINTS+) or the hHIT alone, AICA strokes were missed more frequently when applying the hHIT alone (sensitivity=36.0% [20.2-55.5]) or HINTS without hearing testing (sensitivity=84.0% [65.3-93.6]). However, when applying HINTS+, ruling out cAVS was comparably good for AICA strokes (sensitivity=95.7% [79.0-99.2], n=23) and PICA strokes (sensitivity=99.1% [94.9-99.8], n=107), pointing to added value for bedside hearing testing in AVS.

Diagnostic accuracy in AVS stratified by year of publication—We did not find any change in the diagnostic accuracy of bedside ocular motor testing in AVS in more recent studies (published 2016 or later [502 patients])[16, 22, 23, 25-28] compared to earlier ones (published before 2016 [298 patients])[15, 17, 24] (supplementary Table 4). Importantly, during these two periods, the rate of studies performed by subspecialists vs. non-subspecialists was comparable (subspecialists: 1/3 studies performed before 2016 vs. 2/7 studies performed 2016 or later).

Heterogeneity in HINTS accuracy by individual study

When looking at the range of diagnostic accuracy values reported by individual studies for HINTS, there was significant heterogeneity across studies (HINTS sensitivity range 78.0%-98.8%; specificity range 77.5%-98.6%) (see Figure 3). Machner and colleagues found a particularly low sensitivity of hHIT for central lesions (58%).[28] However, aggregate HINTS sensitivity for cAVS was still 79% (52-92), even in this study.

False negative early MRI-DWI results in included studies

Diagnostic accuracy of early (i.e., within the first 48h) MRI-DWI was assessed in two studies (n=141 stroke patients),[15, 25] with a calculated sensitivity of 85.1% [79.2-91.0]. In one study all but one cAVS patient with initially false-negative MRI-DWIs (15/106, 14.2%) were scanned within the first 48h (2-24 hours: n=9; 24-48 hours: n=5).[15] The one patient had a labyrinthine infarction with a false negative MRI at symptomatic day 5, but went on to develop further AICA-territory infarction in the subsequent week. In the other study all patients received an initial MRI-DWI within the first 24 hours, demonstrating a rate of initially false-negative MRI-DWIs of 17.1% (6/35).[25]

Accuracy of CT and MRI-DWI in AVS from a recent systematic review

The recent systematic review from Shah et al. found accuracy of CT to be substantially lower than MRI-DWI.[18] Comparisons of neuroimaging to ocular motor examination are found in Table 3. Rule out power (LR−) for MRI-DWI was similar to that for hHIT (0.21 MRI-DWI vs. 0.23 hHIT, p=0.56), and both HINTS (0.09, p<0.001) and HINTS+ (0.06, p<0.001) were more potent.

DISCUSSION

In this systematic review, we focused on the diagnostic accuracy of bedside examination to distinguish peripheral from central causes in acutely dizzy patients. We identified ten high-quality (LOE 1-3) and low-risk for bias (QUADAS-2) studies. The best single bedside test for ruling out stroke was the hHIT (LR−=0.23 [0.15-0.36] for a unilaterally abnormal hHIT); based on a recent systematic review of neuroimaging in acute dizziness and vertigo, this value far exceeds CT (LR−=0.79 [0.67-0.92]) and is comparable to MRI-DWI (LR−=0.21 [0.13-0.34]).[18] When hHIT was combined with a search for bilateral, gaze-evoked nystagmus, vertical skew deviation, and new unilateral hearing loss, the composite bedside HINTS+ exam ruled out central causes with high potency (LR−=0.06 [0.02-0.21]) exceeding that of both CT and MRI-DWI from a recent systematic review.[18] Importantly, this was true regardless of the examiner's training background (i.e., sensitivity was comparable between subspecialists and non-subspecialists). To rule in stroke, MRI-DWI was, by far, the best test (LR+=75.13 [20.64-273.76]), but false negatives were frequent (21%) in the first 24-48 hours after onset of symptoms,[18] so ruling out stroke was not as effective as the bedside examination. When present, severe (grade 3) gait/truncal instability was also a strong predictor of stroke (LR+=26.08 [2.67-254.80]). This combination of findings suggests a clear, two-step approach to the diagnostic assessment of AVS—HINTS+ performed by a trained examiner should be the screening battery of choice, and MRI-DWI should be the confirmatory test in those with a central HINTS+ pattern (with only a delayed MRI after 48 hours acceptable to be considered as a "rule out" stroke). In cases where an AVS-patient cannot sit or stand unaided, the eye movement step can be skipped, and the patient referred directly for confirmatory MRI-DWI.

Other bedside findings, when present, also support the presence of a central lesion. These include spontaneous dominantly vertical or torsional nystagmus (LR+=10.85 [2.62-45.00]) or general neurologic examination findings (LR+=26.82 [7.72-93.13]). Regardless of pre-test probability for stroke in AVS, the presence of any such findings leads to a post-test probability that exceeds the typical threshold for pursuing a stroke (or other central) cause (Table 2). However, these tests have low sensitivity (23.1% and 43.6%, respectively, Table 3) and they added no diagnostic value beyond the combination of HINTS+ and gait/truncal stability testing. While it is reasonable to perform these other ocular motor or general neurologic tests for completeness, there is no evidence to suggest they add diagnostic value when a trained examiner can perform HINTS+ testing and assess gait/truncal stability. In situations without a trained examiner in HINTS+ testing, these other tests (which are more familiar to some examiners) may be helpful as an adjunct to assessing gait/truncal stability.

It is important for clinicians to understand when the HINTS family of tests are likely to be falsely negative (i.e., suggesting a peripheral cause of AVS despite presence of a central – mostly vertebrobasilar ischemic - cause). Table 4 stratifies results by stroke location as either in the PICA or AICA territory. It is known that AICA territory strokes are more likely to mimic a peripheral vestibulopathy closely; this is because the AICA generally supplies blood to the inner ear (including labyrinth), vestibular nerve root entry zone, and flocculus,[29] each of which, when infarcted, can lead to a unilaterally abnormal hHIT.[30-33] Accordingly, accuracy of the hHIT alone differs dramatically based on stroke location (PICA=94.5%

vs. AICA=36.0%, p<0.001). Some such AVS-patients have neither gaze-evoked nystagmus nor skew deviation, creating a peripheral pattern HINTS result, despite the presence of a stroke. Therefore, HINTS also has lower sensitivity for AICA strokes (PICA=97.7% vs. AICA=84.0%, p=0.014). Adding a fourth clinical sign (unilateral acute hearing loss) to HINTS (i.e., HINTS+) "rescues" some of these sensitivity losses (HINTS+ AICA=95.7%) (Table 4).

A key finding from this review is that diagnostic accuracy using HINTS remained high even when performed by non-subspecialists. The majority of patients (65%) included in this meta-analysis were assessed by either general neurologists, neurology residents, or ED physicians who received limited training in the assessment of bedside ocular motor signs from experts. Both subspecialists and non-subspecialists demonstrated high accuracy when using HINTS or HINTS+. Sensitivity of HINTS was comparable (94.3% vs. 95.0%, p=0.55), although specificity of HINTS was higher in the subspecialist group than in the non-subspecialist group (97.6% vs. 89.1%, p=0.007), indicating potential differences in the interpretation of test results. Another study which fell outside our inclusion criteria also suggests that trained ED clinicians can accurately perform and interpret the hHIT and nystagmus testing.[34] Thus, our data support the notion that training frontline providers in accurate HINTS testing is possible.[22, 35] However, the precise elements, minimum duration, and need for repeat sessions of this training is currently only partially defined.[22, 34] Importantly, untrained ED clinicians do not appear to perform HINTS testing properly.[36, 37] These findings align with an anticipated clinical practice guideline (GRACE-3) for diagnosis of acute dizziness and vertigo developed by the Society for Academic Emergency Medicine —this will recommend that ED physicians be trained in performance of HINTS testing.[38]

Finally, it is important to consider what imaging recommendations might emerge from this study and the recently published systematic review of neuroimaging in acute dizziness and vertigo.[18] First and foremost, it is clear that head CT scans should play a very limited role in the assessment of AVS or dizziness and vertigo more generally. Sensitivity is lower than even a simple assessment for severe (grade 3) gait/truncal instability (Figure 2), so it is difficult to justify the expense and radiation exposure of CT imaging. Since cerebellar (or other) hemorrhages rarely present with isolated dizziness or vertigo (in almost all cases having some combination of mental status change, dysarthria, or hemiparesis),[39] CT does not seem justified to search for intracerebral hemorrhage in the absence of general neurological examination features. CT may be appropriate in highly selected circumstances (e.g., to rule out hemorrhage definitively prior to thrombolysis[12] or perhaps in a patient who is anticoagulated). If imaging is needed, it should generally be by MRI-DWI. The ideal timing of MRI is less certain. Peak sensitivity of MRI-DWI for posterior fossa strokes is likely 72-100 hours after onset of symptoms,[40] and almost all of the reported false-negative MRI-DWI images included in this review occurred within 48 hours of onset (and the majority within 24 hours). This suggests that if a patient seen within 24-48 hours is stable and neuroimaging would not alter immediate treatment, it might be more cost effective to admit for observation and routine stroke treatments based on HINTS+ results, deferring MRI until the 48-hour mark. Additional studies are needed to determine the optimal imaging timing in the context of a HINTS+ central result.

Limitations

Despite excluding studies with low LOE and high risk for bias or applicability concerns, data sets were heterogeneous both regarding the physicians performing the clinical tests, timing of MR-imaging and the patient characteristics. Lack of structured training and standardized procedures of how to apply these bedside-tests likely increased the inter-individual variability of test performance. In the single study in which ED physicians (who received 6 hours of training twice from expert otologists) performed HINTS testing, the diagnostic accuracy was high when focusing on the AVS cases (62 strokes vs. 26 vestibular neuritis / labyrinthitis cases; sensitivity=96.8% [89.0-99.1]; specificity=84.6% [66.5-93.8]).[22] This illustrates the feasibility of closing an important skill gap previously identified in a prior meta-analysis focusing use of HINTS in the ED setting.[41] As noted, however, the nature and extent of training required is incompletely known. Furthermore, this systematic review did not assess the accuracy of more general approaches to evaluating dizziness and vertigo such as TiTrATE (which divides patients into timing and trigger categories—AVS and other categories) or STANDING (which skips the step of history-taking and algorithmically combines attributes of HINTS testing with positional tests for benign positional vertigo).

While we considered only studies for our meta-analysis that included AVS patients independent from their underlying diagnosis, we found a rate of cAVS of 52.8%, which is higher than the previously estimated fraction of 25±15%,[9] suggesting some enrichment of strokes in the included studies. This most likely reflects selection bias in these studies (perhaps based on referral biases for patients with more vascular risk factors or more frequent neurologic findings). This issue is unlikely to have meaningfully impacted sensitivity estimates for stroke, although it may have inflated specificity estimates somewhat.[42]

CONCLUSIONS

For AVS-patients, HINTS testing outperformed the ABCD2-risk score and early MRI-DWI in correctly identifying stroke, whether performed by subspecialists or non-subspecialists instructed in proper technique. Adding hearing assessment (HINTS+) improved identification in the subgroup with AICA strokes substantially. Severe (grade 3) gait/truncal instability (i.e., inability to sit/stand unassisted) further supports a diagnosis of stroke with high specificity and may help to identify rare patients with AICA strokes in whom HINTS+ is falsely peripheral. Despite strong evidence to support their validity, use of these bedside approaches has not been widely disseminated to non-subspecialist clinicians. Improved training in HINTS+ techniques would likely result in better diagnostic accuracy for acutely dizzy patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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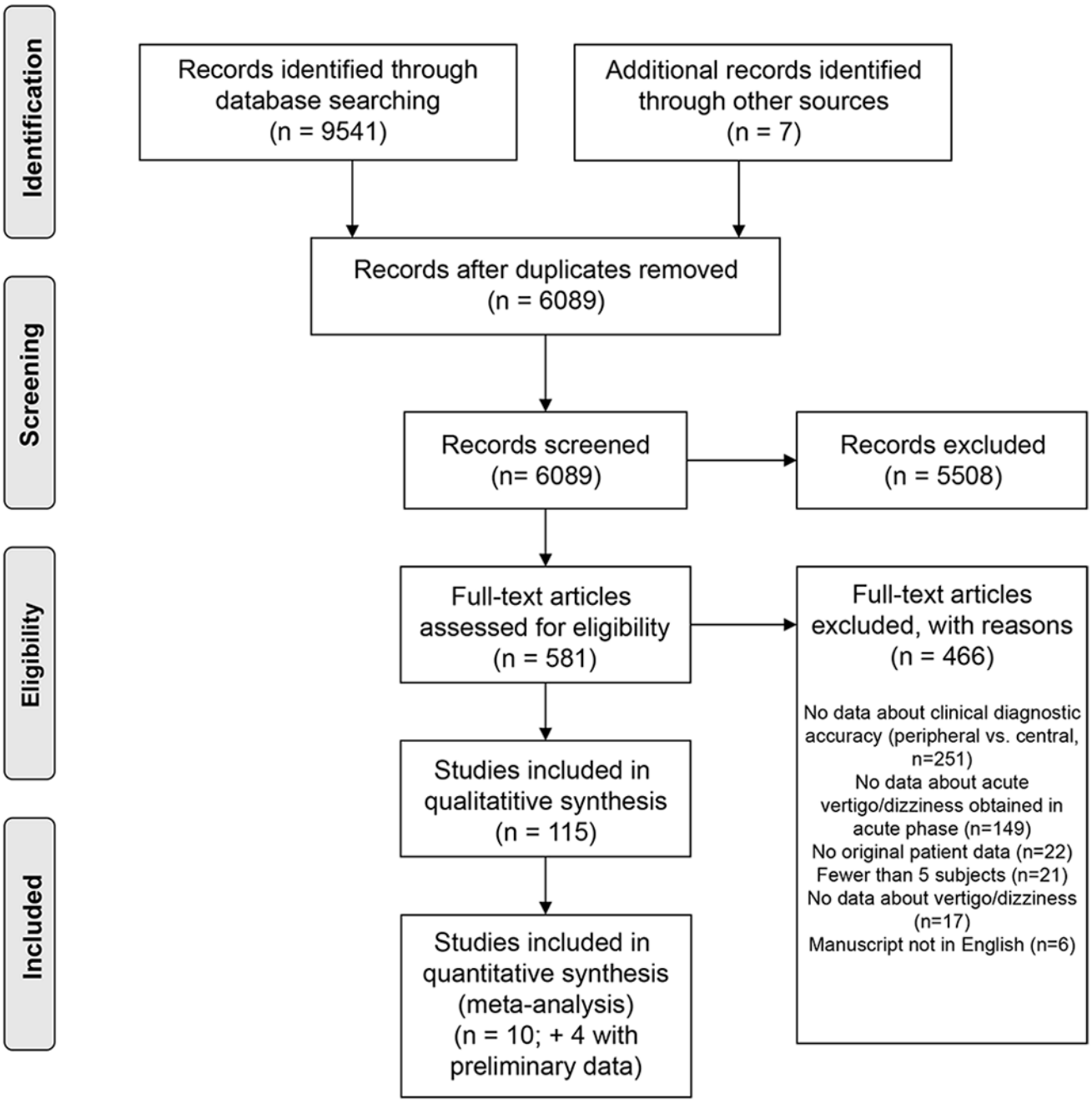

Figure 1:
Prisma flow chart, modified after[43]

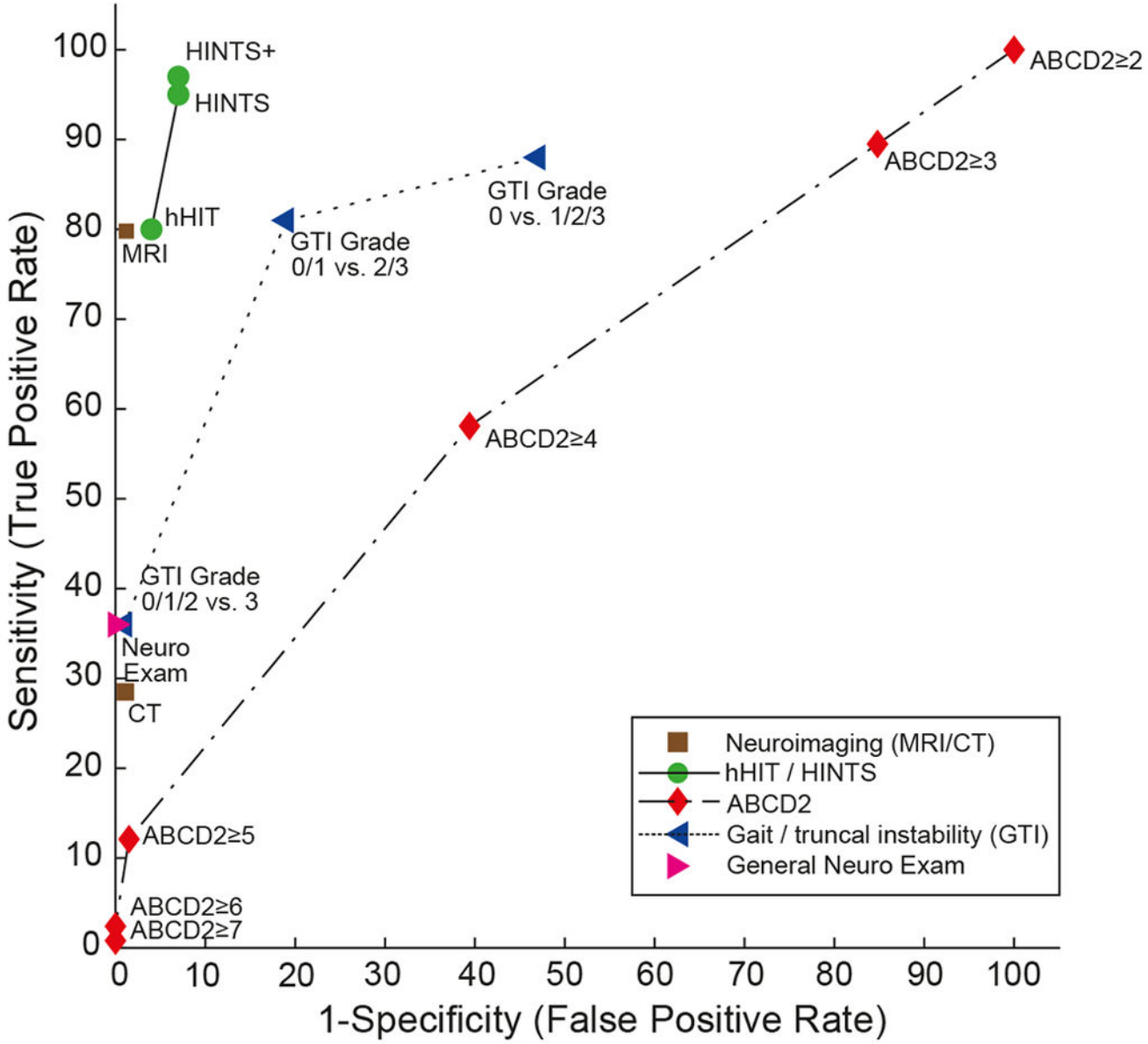

Figure 2:

Summary receiver operating characteristic (SROC) curve analysis for the “HINTS (Head Impulse, Nystagmus, Test of Skew) family” compared with neuroimaging (computed tomography [CT] or magnetic resonance imaging with diffusion-weighted sequences [MRI-DWI], values used as published by Shah and colleagues[6]), graded gait/truncal instability (GTI) ratings, general neurologic exam and vascular risk stratification by ABCD2 (age, blood pressure, clinical features, duration of symptoms, diabetes) score (data from a single study[15]) for detecting stroke in patients presenting the acute vestibular syndrome (modified after[44]).

SROC curves are shown for five different diagnostic approaches to diagnosing stroke in the acute vestibular syndrome. A perfect test or decision rule has threshold cutoffs in the upper left corner (100% sensitivity, 100% specificity) and an area under the curve (AUC)

of 1.0. Note that the gait/truncal instability ratings outperform the ABCD2 score and the general neurologic exam but are clearly inferior compared to the HINTS family of eye movement tests. Both HINTS and HINTS plus (HINTS plus new hearing loss detected by finger rubbing or similar) demonstrate a higher diagnostic accuracy for ruling out stroke than MRI including DWI.

Abbreviations: hHIT=horizontal head-impulse test

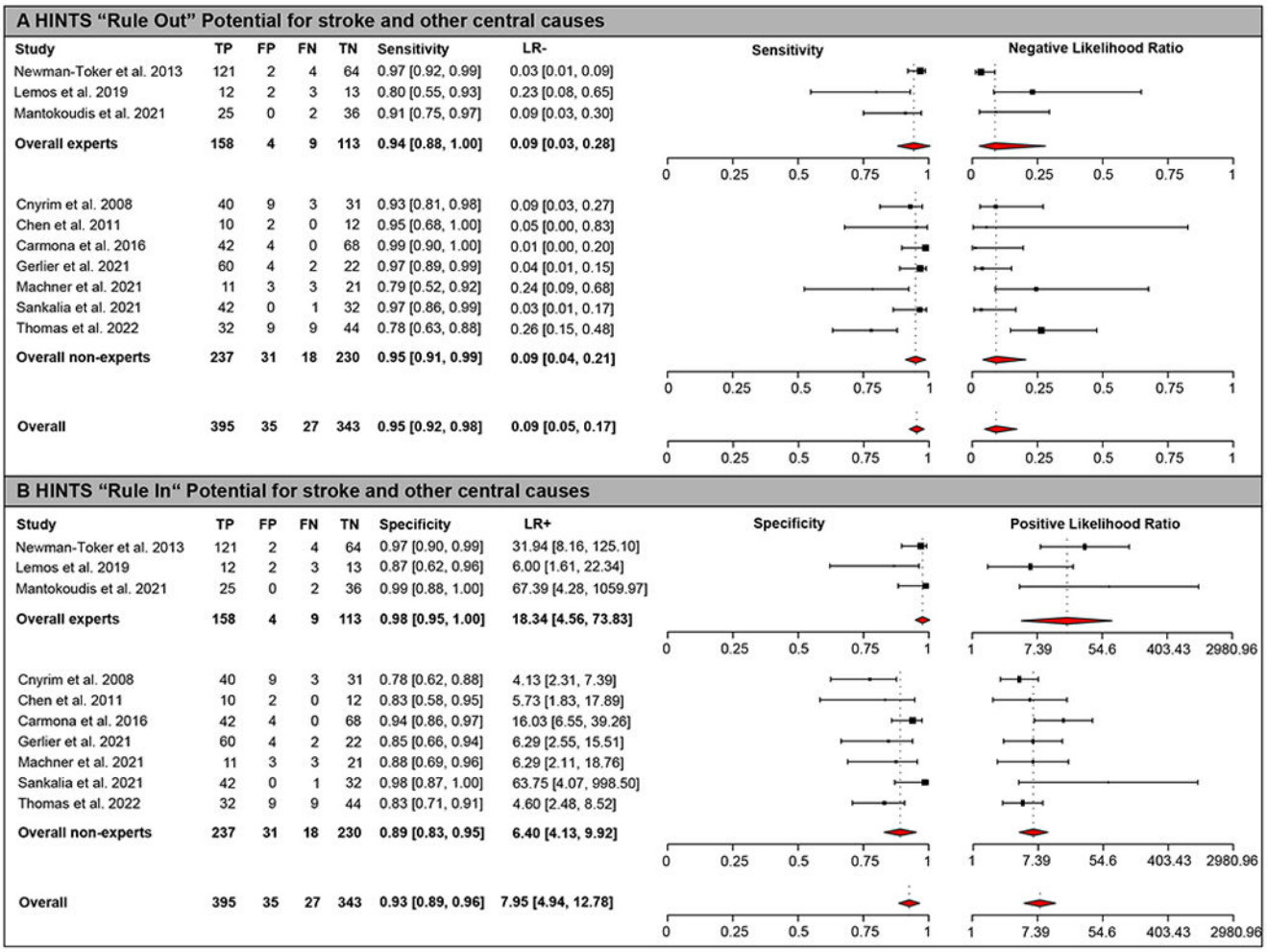

Figure 3:

Forest plots of diagnostic test properties for HINTS (Head Impulse, Nystagmus, Test of Skew). Panel A – sensitivity and negative likelihood ratio (LR−) including 95% confidence intervals (CI); Panel B – specificity and positive likelihood ratio (LR+) including 95% CI. Studies are grouped according to subspecialty status (neuro-otology / neuro-ophthalmology subspecialists vs. non-subspecialists [i.e., trained general neurologists, neurology residents, emergency physicians]) and aggregated values for all test properties (including 95% CI) are provided for both subgroups separately and for all studies included (n=10). Summary measures were calculated using a random effects model using the DerSimonian-Laird estimator.[45, 46] Heterogeneity amongst all studies was significant both for ruling out (i.e., sensitivity, p=0.044) and for ruling in (i.e., specificity, p=0.003) central (mostly vertebrobasilar ischemic stroke) causes using Cochran's Q. Note that the axis for positive likelihood ratio uses an exponential scale.

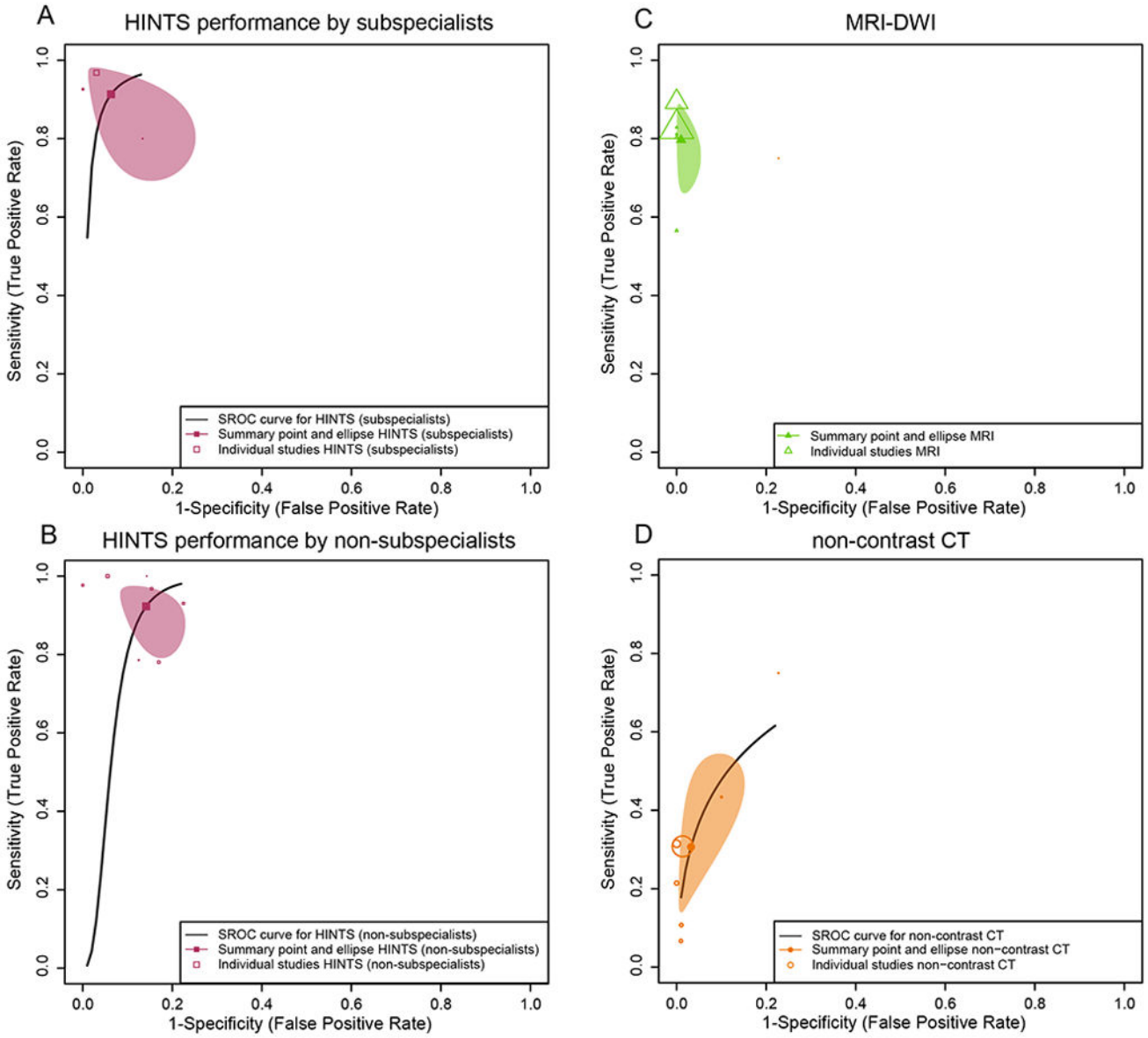

Figure 4:

Summary ROC (SROC) curves for HINTS when performed by subspecialist neurologists trained in either neuro-otology or neuro-ophthalmology (subspecialists, panel A, n=3 studies) or by general or stroke neurologists or trained emergency medicine physicians (non-subspecialists, panel B, n=7 studies). Both individual study results (empty squares) and overall point estimates (filled square, including the 95% confidence ellipse) for HINTS are provided. For comparison MRI-DWI (panel C, n=5 studies, filled triangle, data retrieved from[18]) and non-contrast CT (panel D, n= 6 studies, filled circle, data retrieved from[18]) data, again including both individual studies and overall point estimates (including 95% confidence ellipses) are provided. For single studies, the size of squares, circles or triangles is proportional to the study sample size. Note that sensitivity and specificity (including 95% CI) for MRI and CT data as included in the paper by Shah and colleagues,[18]

has been recalculated with the same random effects model (using the DerSimonian-Laird estimator[45, 46]) as used for the diagnostic accuracy parameters of the HINTS. Note that the right end of the SROC curve for the non-subspecialists (panel B) is extremely steep, causing slight changes in horizontal value and appears to cover a long range on the vertical level. Note also that when calculating the SROC-curve for the MRI-DWI data (panel C), no stable result for the fit could be achieved, likely because the 5 studies included have specificities very close to each other.

Abbreviations: CT=computed tomography; DWI=diffusion weighted imaging; HINTS=Head Impulse, Nystagmus, Test of Skew; MRI=magnetic resonance imaging; SROC=summary receiver operating characteristic.

Table 1:

epidemiologic information on the included studies

	Number of studies	cAVS patients (n)	pAVS patients (n)
Age (range of mean ages) [yrs]	9[15, 16, 21-24, 26-28]	53±17 - 71.8±14.9	43.3±14.9 - 72.8±9.5
Gender*	9[15, 16, 21-24, 26-28]		
Females		161	172
Males		218	194
Central etiology			
ischemic	10[15, 16, 21-28]	334	N/A
PICA	5[15, 16, 26-28]	128	N/A
AICA	4[15, 16, 26, 27]	25	N/A
SCA	3[15, 27, 28]	8	N/A
Brainstem	3[15, 27, 28]	32	N/A
Non-specified vascular territory	7[21-26, 28]	141	N/A
hemorrhagic	2[15, 21]	15	N/A
other central†	5[15, 21, 22, 24, 25]	73	N/A
all	10[15, 16, 21-28]	422	N/A
Peripheral etiology			
Vestibular neuritis	10[15, 16, 21-28]	N/A	377
Labyrinthitis	1[15]	N/A	1
all	10[15, 16, 21-28]	N/A	378
Clinical presentation – isolated AVS vs. non-isolated AVS			
Both iAVS and niAVS	5[15, 25-28]	224	173
niAVS		76 (34%)	0 (0%)
iAVS		148 (66%)	173 (100%)
iAVS only	5[16, 21-24]	198	205
Bedside vestibular testing performed			
Horizontal head impulse test	10 [10, 10][15, 16, 21-28]	422	378
Direction-changing Nystagmus on lateral gaze	10 [10, 10][15, 16, 21-28]	400	376
Alternating cover test‡	10 [9, 10][15, 16, 21-28]	421	354
HINTS battery	10 [10, 10][15, 16, 21-28]	422	378
HINTS-plus battery	6 [6, 6][15, 16, 22, 23, 25, 27]	276	252
Gait/truncal instability rating§	3 [3, 3][15, 16, 23]	177	152
Testing for hearing loss	6 [6, 6][15, 16, 22, 23, 25, 27]	276	252
Vertical or torsional SN	3 [3, 3][15, 23, 26]	162	115
Saccadic vertical smooth pursuit eye movements	2 [2, 2][23, 24]	53	54
Imaging			
initial MRI (+DWI) false negative for ischemic stroke	2[15, 25]	21 / 141 (14.9%)‖	N/A

[*] In one study the gender is not reported (n=75).[25]

[†] Other central included vestibular migraine (n=29), multiple sclerosis (n=21), cerebellar tumors (n=6), cerebellar atrophy (n=3), paraneoplastic syndromes (n=2), Acute obstructive hydrocephalus (n=1), Wernicke's encephalopathy (n=1), cerebellar metastasis from breast cancer (n=1), carbamazepine intoxication (n=1), non-specified (n=8).

[‡] In one study a positive skew deviation was an exclusion criterion for the pAVS cohort. From this study the SD numbers were included only for the cAVS cohort.[28]

[§] One study only provided a rating for no ataxia vs. severe (grade 3) truncal ataxia.[23] From another study, truncal ataxia ratings were not previously published and were provided via personal communication with the corresponding author.[15]

[‖] False negative strokes on early MRI-DWI were located in the dorsal/lateral medulla (n=11), the middle cerebellar peduncle (n=2), the pontomesencephalic junction (n=1) or cerebellar (n=1). In 6 patients stroke locations were not specified.

Abbreviations: AICA=anterior inferior cerebellar artery; APV=acute peripheral vestibulopathy; AVS=acute vestibular syndrome; C=central; cAVS=central acute vestibular syndrome; DWI=diffusion-weighted imaging; EM=eye movements; HINTS=Head Impulse test, Nystagmus examination, Test of Skew; HINTS plus=HINTS plus new unilateral hearing loss; iAVS=isolated acute vestibular syndrome; MRI=magnetic resonance imaging; N/A=not available; niAVS=non-isolated acute vestibular syndrome; P=peripheral; pAVS=peripheral acute vestibular syndrome; PICA=posterior inferior cerebellar artery; SCA=superior cerebellar artery; SN=spontaneous nystagmus.

Table 2.

Diagnostic likelihood ratios for bedside tests in AVS, with post-test probability of stroke

Diagnostic Test	Likelihood Ratio (95% CI)	Post-Test Probability Stroke (%) given Incidence (Pre-Test Probability) in AVS			
To "Rule Out"	***Negative LR***	***10%***	***25%***	***50%***	***75%***
HINTS+ peripheral	0.06 (0.02-0.21)	0.7	2.0	5.7	15.3
HINTS peripheral	0.09 (0.05-0.17)	1.0	2.9	8.3	21.3
HIT unilaterally abnormal	0.23 (0.15-0.36)	2.5	7.1	18.7	40.8
Gait/truncal instability (grade 0-2)†	0.62 (0.40-0.97)	6.4	17.1	38.3	65.0
General neuro exam normal	0.57 (0.43-0.76)	6.0	16.0	36.3	63.1
CT negative (from Shah et al.[18])	0.79 (0.67-0.92)	8.1	20.8	44.1	70.3
MRI-DWI negative (from Shah et al.[18])	0.21 (0.13-0.34)	2.3	6.5	17.4	38.7
To "Rule In"	***Positive LR***	***10%***	***25%***	***50%***	***75%***
HINTS+ central *	8.47 (3.66-19.56)	48.5	73.8	89.4	96.2
HINTS central *	7.95 (4.94-12.78)	46.9	72.6	88.8	96.0
HIT bilaterally normal *	7.89 (4.63-13.47)	46.7	72.5	88.8	95.9
Gait/truncal instability (grade 3)†	26.08 (2.67-254.80)	74.3	89.7	96.3	98.7
General neuro exam abnormal	26.82 (7.72-93.13)	74.9	89.9	96.4	98.8
CT abnormal (from Shah et al.[18])	9.88 (3.11-31.39)	52.3	76.7	90.8	96.7
MRI-DWI abnormal (from Shah et al.[18])	75.17 (20.64-273.76)	89.3	96.2	98.7	99.6

*Note it is not plausible that the true value of specificity (and corresponding positive LR) for HINTS+ (*with* testing for hearing loss) is actually higher than specificity for HINTS (*without* testing for hearing loss). This is because adding another test to a clinical decision rule or composite score using a Boolean logical 'or' (rather than 'and') can at best maintain the rule's specificity, and typically would lower it. The measured difference seen here reflects the fact that only a subset of studies reporting on HINTS also reported on HINTS+ (as reflected in the wider 95% CI for HINTS+ positive LR). It is expected therefore that the measured HINTS+ positive LR is a slight overestimate (or that for HINTS is a slight underestimate). The same logic applies to the difference between HINTS (*with* nystagmus and skew testing) and HIT alone (*without* nystagmus or skew testing). Either HINTS positive LR is a slight overestimate (or that for HIT is an underestimate). Importantly, however, the impact of these differences on estimates of post-test stroke probability are likely small.

†Note that assessment technique and timing may matter—Carmona et al.[16] performed the testing right at the beginning of the clinical evaluation and their pAVS subjects performed significantly worse than in the Newman-Toker et al. cohort,[15] where testing was performed after patients sat for about 10 minutes (in this latter study, none of the pAVS patients had abnormal gait/truncal stability as gauged by ability to stand or sit independently). Whether other potential confounders may have been present to explain the differences (e.g., whether patients had received vestibular suppressant medications) is unknown.

Abbreviations: AVS=acute vestibular syndrome; CI = confidence interval; CT=computed tomography; HINTS=head impulse, nystagmus, test of skew; HINTS+=HINTS plus new unilateral hearing loss; HIT; LR=likelihood ratio; MRI-DWI=magnetic resonance imaging with diffusion-weighted imaging.

Table 3.

Bedside tests and neuroimaging diagnostic accuracy in AVS

Test	Sensitivity % (95% CI)	LR− (95% CI)	Specificity % (95% CI)	LR+ (95% CI)
hHIT	79.9 (72.2-87.5)	0.23 (0.15-0.36)	95.6 (92.7-98.5)	7.89 (4.63-13.47)
HINTS	95.3 (92.5-98.1)	0.09 (0.05-0.17)	92.6 (88.6-96.5)	7.95 (4.94-12.78)
HINTS+	97.2 (94.0-100.0)	0.06 (0.02-0.21)	92.4 (86.9-97.9)	8.47 (3.66-19.56)
Grade 3 GTI	35.8 (5.2-66.5)	0.62 (0.40-0.97)	99.2 (97.8-100.0)	26.08 (2.67-254.80)
Any obvious signs	43.6 (24.9-62.2)	0.57 (0.43-0.76)	98.9 (97.3-100.0)	26.82 (7.72-93.13)
CT	28.9 (13.1-44.7)	0.79 (0.67-0.92)	99.4 (98.6-100.0)	9.88 (3.11-31.39)
MRI-DWI	81.1 (73.3-88.8)	0.21 (0.13-0.34)	99.9 (99.6-100.0)	75.17 (20.64-273.76)

Abbreviations: CI=confidence interval; CT=computed tomography; DWI=diffusion-weighted; GTI=gait/truncal instability; hHIT=horizontal head impulse test; HINTS=Head Impulse, Nystagmus, Test of Skew; HINTS ‘plus,’=HINTS plus new hearing loss detected by finger rubbing; LR=likelihood ratio; MRI=magnetic resonance imaging.

Table 4:

Diagnostic test properties for stroke in AVS, stratified by stroke location

Diagnostic Test Parameter	PICA Strokes % or LR (95% CI)	AICA Strokes % or LR (95% CI)	p-value (Fisher's exact)*
Sensitivity			
HINTS+	99.1% (94.9-100.0) (n=107)	95.7% (79.0-99.2) (n=23)	0.324
HINTS	97.7% (93.3-99.2) (n=128)	84.0% (65.3-93.6) (n=25)	0.014
hHIT	94.5% (89.1-97.3) (n=128)	36.0% (20.2-55.5) (n=25)	<0.001
Gait/truncal instability (grade 3)†	49.5% (40.1-59.0) (n=103)	52.3% (32.7-71.2) (n=21)	1.000
General neuro exam	41.8% (32.4-51.7) (n=96)	46.9% (25.5-69.4) (n=15)	0.782
Likelihood Ratio (−)			
HINTS+	0.01 (0.00-0.07)	0.05 (0.01-0.31)	0.271
HINTS	0.03 (0.01-0.08)	0.17 (0.07-0.41)	0.009
hHIT	0.06 (0.03-0.12)	0.67 (0.50-0.89)	<0.001
Gait/truncal instability (grade 3)†	0.51 (0.42-0.61)	0.50 (0.31-0.74)	0.818
General neuro exam	0.59 (0.49-0.69)	0.53 (0.34-0.85)	0.715
Specificity ‡,§			
HINTS+	94.8% (90.0-97.3) (n=153)	94.8% (90.0-97.3) (n=153)	1.000
HINTS	94.8% (91.0-97.1) (n=213)	95.8% (91.9-97.8) (n=189)	0.815
hHIT	95.3% (91.6-97.4) (n=213)	96.3% (92.6-98.2) (n=189)	0.805
Gait/truncal instability (grade 3)†	99.6% (96.6-100.0) (n=138)	99.6% (96.6-100.0) (n=138)	1.000
General neuro exam	99.6% (96.7-100.0) (n=141)	99.6% (96.1-100.0) (n=117)	1.000
Likelihood Ratio (+)			
HINTS+	18.95 (9.65-37.21)	18.29 (9.27-36.12)	0.943
HINTS	18.91 (10.63-33.64)	19.85 (9.86-39.94)	0.917
hHIT	20.14 (10.98-36.93)	9.72 (3.97-23.80)	0.187
Gait/truncal instability (grade 3)†	137.66 (8.60-2204.88)	145.32 (8.88-2378.93)	0.979
General neuro exam	118.58 (7.38-1905.41)	110.63 (6.63-1846.11)	0.973

*P values for sensitivity and specificity comparisons are based on Fisher's exact test. P values for positive and negative diagnostic likelihood ratios are calculated based on asymptotic approximation for unpaired tests.[47]

†Note that assessment technique and timing may matter—Carmona et al.[16] performed the testing right at the beginning of the clinical evaluation and their pAVS subjects performed significantly worse than in the Newman-Toker et al. cohort,[15] where testing was performed after patients sat for about 10 minutes (in this latter study, none of the pAVS patients had abnormal gait/truncal stability as gauged by ability to stand or sit independently).

‡The minor differences in the point estimate and the 95% confidence interval for the specificity values for HINTS, HIT and general neuro exam reported here are due to the fact that one study reported on PICA strokes and peripheral AVS only,[28] and thus the number for pAVS cases in the PICA and AICA subgroups for HINTS, HIT and general neuro exam are different.

§Because of differences in the included studies for HINTS+ calculations, specificity for PICA and AICA subgroups may appear to be higher than in the main results, but within the subgroup HINTS+ had always an equivalent or slightly lower specificity.

Abbreviations: AICA=anterior inferior cerebellar artery; CI=confidence interval; hHIT=horizontal head impulse test; HINTS=Head Impulse, Nystagmus, Test of Skew; OR=odds ratio; PICA=posterior inferior cerebellar artery.