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Does This Patient Have Acute Mountain Sickness?
The Rational Clinical Examination Systematic Review

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IMPORTANCE Acute mountain sickness (AMS) affects more than 25% of individuals ascending to 3500 m (11 500 ft) and more than 50% of those above 6000 m (19 700 ft). AMS may progress from nonspecific symptoms to life-threatening high-altitude cerebral edema in less than 1% of patients. It is not clear how to best diagnose AMS.

OBJECTIVE To systematically review studies assessing the accuracy of AMS diagnostic instruments, including the visual analog scale (VAS) score, which quantifies the overall feeling of sickness at altitude (VAS[O]; various thresholds), Acute Mountain Sickness-Cerebral score (AMS-C; ≥0.7 indicates AMS), and the clinical functional score (CFS; ≥2 indicates AMS) compared with the Lake Louise Questionnaire Score (LLQS; score of ≥5).

DATA EXTRACTION AND SYNTHESIS Searches of MEDLINE and EMBASE from inception to May 2017 identified 1245 publications of which 91 were suitable for prevalence analysis (66 944 participants) and 14 compared at least 2 instruments (1858 participants) using a score of 5 or greater on the LLQS as a reference standard. To determine the prevalence of AMS for establishing the pretest probability of AMS, a random-effects meta-regression was performed based on the reported prevalence of AMS as a function of altitude.

MAIN OUTCOMES AND MEASURES AMS prevalence, likelihood ratios (LRs), sensitivity, and specificity of screening instruments.

RESULTS The final analysis included 91 articles (comprising 66 944 study participants). Altitude predicted AMS and accounted for 28% of heterogeneity between studies. For each 1000-m (3300-ft) increase in altitude above 2500 m (8200 ft), AMS prevalence increased 13% (95% CI, 9.5%-17%). Testing characteristics were similar for VAS(O), AMS-C, and CFS vs a score of 5 or greater on the LLQS (positive LRs: range, 3.2-8.2; $P = .22$ for comparisons; specificity range, 67%-92%; negative LRs: range, 0.30-0.36; $P = .50$ for comparisons; sensitivity range, 67%-82%). The CFS asks a single question: "overall if you had any symptoms, how did they affect your activity (ordinal scale 0-3)?" For CFS, moderate to severe reduction in daily activities had a positive LR of 3.2 (95% CI, 1.4-7.2) and specificity of 67% (95% CI, 37%-97%); no reduction to mild reduction in activities had a negative LR of 0.30 (95% CI, 0.22-0.39) and sensitivity of 82% (95% CI, 77%-87%).

CONCLUSIONS AND RELEVANCE The prevalence of acute mountain sickness increases with higher altitudes. The visual analog scale for the overall feeling of sickness at altitude, Acute Mountain Sickness-Cerebral, and clinical functional score perform similarly to the Lake Louise Questionnaire Score using a score of 5 or greater as a reference standard. In clinical and travel settings, the clinical functional score is the simplest instrument to use. Clinicians evaluating high-altitude travelers who report moderate to severe limitations in activities of daily living (clinical functional score ≥2) should use the Lake Louise Questionnaire Score to assess the severity of acute mountain sickness.

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Clinical Scenario

A 52-year-old healthy man living at sea level arrives at a hotel at 4000 m (13 100 ft) after traveling all day. This is his first exposure to an altitude above 2500 m (8200 ft). When walking to dinner that evening he feels unusually exhausted, has shortness of breath and dizziness, and experiences palpitations and nausea. He is unable to eat and must return to his room. Which diagnostic instruments can be used to determine if these symptoms are indicative of severe acute mountain sickness (AMS)?

Key Points

Question What is the best instrument to use for diagnosing acute mountain sickness (AMS)?

Findings In a systematic review of studies assessing the accuracy of existing AMS diagnostic instruments, the visual analog scale for the overall feeling of sickness at altitude (VAS[O]) score, the Acute Mountain Sickness-Cerebral score (AMS-C), and the clinical functional score (CFS) had similar testing characteristics for diagnosing AMS as did a reference standard (the Lake Louise Questionnaire Score [LLQS] using ≥5 to indicate a positive test result).

Meaning Although these instruments emphasize different clinical features, they all performed similarly for establishing a diagnosis of AMS. The clinical functional score is the simplest instrument to use for diagnosing AMS because it relies on a single question and emphasizes functional limitations resulting from AMS.

Traveling to high altitude for recreational purposes has become increasingly popular but risks the development of AMS. AMS affects more than 25% of individuals ascending to 3500 m (11 500 ft) and more than 50% of those reaching elevations above 6000 m (19 700 ft).[1-3] AMS affects otherwise healthy persons, develops within hours after arriving at altitude, and results in functional impairment from symptoms that may include headache, anorexia, nausea, vomiting, dizziness, fatigue, and sleep disturbances.[4] In the vast majority of cases, these symptoms resolve spontaneously after 18 to 36 hours without requiring (curative) descent to lower altitude, but in fewer than 1% of individuals with AMS, the disease progresses to life-threatening high-altitude cerebral edema manifested by an altered level of consciousness and ataxia.

AMS *acute mountain sickness*

AMS-C *AMS-Cerebral score*

CFS *clinical functional score*

LLQS *Lake Louise Questionnaire Score*

VAS *visual analog scale*

VAS(O) *VAS for the overall feeling of mountain sickness*

The pathophysiology of AMS and high-altitude cerebral edema is not fully understood. Exaggerated cerebral vasodilation, increased sympathetic activity, diminished hypoxic ventilatory drive, severe hypoxemia (especially during sleep), increased salt and water retention, and increased oxidative stress and inflammation all may contribute to the development of AMS.[4-7]

Identified risk factors for AMS can be grouped in the following ways: (1) an individual's health, physiology, and genetics; and (2) specific behaviors and activities performed at high altitude. Although a recent meta-analysis challenged this concept,[8] the most widely recognized risk factor is an individual person's susceptibility to AMS. After a first episode of AMS, the risk of recurrence following reascent in similar conditions (rapidity of ascent, absolute altitude, no medical prophylaxis) can be as high as 60% with an odds ratio (OR) of as much as 12. Estimates of this risk vary by the type of diagnostic instrument used to establish a diagnosis of AMS.[9-15] Although not yet demonstrated in humans, animal studies suggest that individual susceptibility to AMS can be explained by genetic differences in the respiratory drive.[16-18] The risk for AMS is as much as 2.06-fold (95% CI, 1.15-3.72) lower for people older than 50 years.[12,14,19-22] Women may be more likely affected than men,[19,22,23] but this finding is not consistent.[11,13,14,24] Medical conditions such as migraine,[10,11,25] obesity,[22,26] and mood states (anxiety) might also play a role in the development of AMS,[27] whereas smoking and alcohol consumption do not appear to increase the risk for AMS.[3,20,28]

The most important modifiable behaviors at altitude that can influence the risk of developing AMS are the altitude attained and speed of ascent.[9,11,15,20] Ascents that are faster than 400 m per day (1300 ft/d) have an OR of 4.69 (95% CI, 2.79-7.90), whereas slower ascents have an OR of 0.30 (95% CI, 0.20-0.44) for the development of AMS. AMS is less likely to develop when there has been preacclimatization (ie, previous exposure to altitude within 1-2 months)[9,14,19,20] or medical prophylaxis with acetazolamide or dexamethasone.[29-31] In contrast, physical training does not reduce the risk for developing AMS.[11,12,15,20,26,32]

There are no biomedical tests that can establish a diagnosis of AMS; consequently, the diagnosis is made from clinical features. AMS is characterized by subjective symptoms (headache, anorexia, nausea, sometimes vomiting, dizziness, fatigue, and sleep disturbances) and, less frequently, few objective clinical signs (ataxia, palpitations, pulmonary rales, cyanosis) reported by the affected individual or through observations made by travel companions of persons with AMS.[16] The presence and intensity of these altitude-related symptoms, their associated functional impairment, or both are assessed using a variety of diagnostic instruments. The Acute Mountain Sickness-Cerebral score (AMS-C), the Hackett clinical score, and the Lake Louise Questionnaire Score (LLQS) are the instruments used most frequently to establish a diagnosis of AMS. Each of these instruments was derived from a previous non-altitude-specific Environmental Symptoms Questionnaire III score and are calculated as the sum of values given to different symptoms and signs weighted by their severity. Different cutoff values have been used to establish a diagnosis of AMS using the LLQS. In general, values larger than 5 points have been considered diagnostic of moderate to severe AMS. The Chinese AMS score, also based on the presence of several symptoms, is almost exclusively used in China. A visual analog scale (VAS) score, quantifying the subjective feeling of overall severity of sickness at altitude (VAS[O]), is the most recent instrument to be used for diagnosing AMS and has no commonly accepted cutoff value. The clinical functional score (CFS) is the simplest instrument to use because it relies on a single question: "Overall if you had any symptoms, how did they affect your daily activity?" scored on an ordinal scale of 0 to 3 (**Table 1** and eAppendix 1 in the Supplement). Despite several of these instruments

Table 1. Summary of Acute Mountain Sickness Diagnostic Scoring Systems

Lake Louise Questionnaire Score[a]		AMS-C[b]		Hackett Clinical Score[c]			Chinese AMS Score[e]		Clinical Functional Score[f]	
Symptom	Value	Symptom	Weight	Symptom	Value	VAS Scores[d]	Symptom	Value	Symptom	Value
Headache										
Headache	0-3	Headache	0.465	Headache	1	Headache	Headache	1-7		
				Headache not relieved by painkillers	2					
Gastrointestinal										
Gastrointestinal symptoms	0-3	Loss of appetite	0.413	Nausea, anorexia, or both	1	Gastrointestinal symptoms	Vomiting	2-7		
		Sick to stomach	0.347	Vomiting	2		Nausea	1		
							Anorexia	1		
							Abdominal distension	1		
							Diarrhea, constipation, or both	1		
Neurological										
Dizziness, lightheadedness, or both	0-3	Coordination off	0.519	Dizziness	1	Dizziness, lightheadedness, or both	Dizziness, lightheadedness, or both	1		
		Dim vision	0.501	Ataxia	2		Dazzling or blurred vision	1		
		Lightheaded	0.489				Numbness of the extremities	1		
		Dizzy	0.446							
		Faint	0.346							
Fatigue										
Fatigue, weakness, or both	0-3	Feeling weak	0.387			Fatigue, weakness, or both	Lethargy	1		
Difficulty sleeping	0-3			Difficulty sleeping	1	Trouble sleeping	Insomnia	1		
Respiratory										
				Shortness of breath at rest	1		Palpitation	1		
				Pulmonary rales 1 location	1		Shortness of breath	1		
				Peripheral edema	1		Chest distress	1		
				Tachypnea >25/min	2		Cyanosis of the lips	1		
				Pulmonary rales >1 location	2					
Overall										
		Feeling sick	0.692			Overall severity of AMS symptoms			No reduction of daily activity	0
		Feeling hungover	0.584						Mild reduction	1
									Moderate reduction	2
									Severe reduction (bed rest)	3

Abbreviations: AMS, acute mountain sickness; AMS-C, AMS-Cerebral score; VAS(C), visual analog scale-composite; VAS(O), VAS for the overall feeling of mountain sickness; VAS(I), VAS for each item of AMS.

[a] Score requires the presence of headache (the other instruments do not) and at least 1 other symptom to establish an AMS diagnosis. Symptom grades: 0, no symptoms; 1, mild; 2, moderate; 3, severe. Final score is based on the sum of all individual symptoms (a score of ≥3, ≥4, or ≥5 indicates AMS).

[b] Score is derived from the Environmental Symptoms Questionnaire III. Respondents indicate how they were feeling that day on a scale of 0 (no symptoms) to 5 (most-severe symptoms). Final score = the sum of each symptom score × the weight given each symptom/25.95 × 5. A score greater than or equal to 0.7 indicates AMS.[33]

[c] Score is derived from a clinician's assessment of each symptom. Final score is based on the sum of all individual symptoms (a score of ≥3 indicates AMS).[34]

[d] Similar to VAS scores used in other contexts (eg, pain management), the patient places a single slash mark on a 100-mm long horizontal line for each VAS (ranging from 0 [none] to 100 [severe]). This indicates either the overall severity (VAS[O]), or each symptom/item (VAS[I]), which are then combined in the composite score (VAS[C]). Various cutoffs are used depending on the different studies, as no current standard cutoff is defined. VAS(C) is mentioned for completeness but was not used in the analysis due to lack of data.[35]

[e] Score classifies the severity of headache with 1 (not present), 2, 4, or 7 points (severe), and the severity of vomiting from 2 points (vomiting 1-2 times per day) to 7 points (vomiting >5 times a day). The presence of other symptoms counts as 1 point each. Presence of headache, vomiting, or a total score of 5 indicates AMS.[36]

[f] CFS does not query regarding individual symptoms. Asks if the patient had any symptoms and how did the symptoms affected their activity on a scale of 0 to 3 (a score of ≥2 indicates AMS).[37]

having been extensively used in clinical and research settings, how they perform relative to one another has not been studied in detail.

We compared the relative performance of the instruments used to diagnose AMS against what is commonly considered a reference standard, the LLQS, using its highest threshold of 5 points or greater to establish a diagnosis of severe AMS, which is associated to a higher risk of developing life-threatening high-altitude cerebral edema.[24] Because use of a diagnostic test requires knowing the pretest probability of a disease being present, we reviewed the literature regarding the presence of AMS as a function of altitude.

Methods

Literature Search Strategy

The PRISMA Statement was followed to systematically review published literature on AMS (eFigure in the Supplement). MEDLINE and EMBASE were searched from inception to May 22, 2017, without language restriction to identify AMS in unselected visitors to high altitude. Keywords from the Rational Clinical Examination search strategy[38] were combined with the MeSH keywords *acute mountain sickness* and *altitude sickness* (eAppendix 2 in the Supplement). Additional relevant articles were identified from searching the bibliographies of retrieved articles. Original studies that reported epidemiological data, described diagnostic procedures, or included comparison of different diagnostic instruments (including both observational and intervention study designs) were included. Review articles, studies that lacked clinical data, those in which the diagnostic procedure was not clearly defined, and those dealing exclusively with children or adolescents were excluded. High-altitude pulmonary edema (a separate entity from AMS that has different pathophysiological mechanisms) was not reviewed.[39] Each abstract was reviewed independently by 2 authors (D.M. and T.-H.C.) to ensure that relevant publications met inclusion criteria. Subsequently, these same investigators independently reviewed each full-text article to confirm that inclusion and exclusion criteria were met and also abstracted data from the included studies. Disagreements were resolved by discussion, and, when necessary, consensus was reached with a third author (C.S.).

Data Extraction From Selected Articles and Quality Ratings

From each selected article, data on the prevalence of AMS, altitude above sea level, and the diagnostic instrument(s) used were extracted. If necessary, additional data were obtained by contacting the authors of the original studies.

For eligible studies, the risk of bias and applicability concerns were evaluated using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) criteria[40] by 2 coauthors (D.M. and T.-H.C.). The items or domains in QUADAS-2 were labeled as unknown if the corresponding study characteristics were not reported. Disagreements in quality assessment were resolved by consensus among coauthors.

Choice of Reference Standard

To compare different instruments, the LLQS was selected as the reference instrument based on expert opinion and because the LLQS has become the most frequently studied comparator scale. Expert opinion is that a threshold score of 3 or greater enhances the opportunity to detect mild AMS but may result in overdiagnosis. Most studies evaluated the LLQS at various cutoffs. For the present review, the highest cutoff (a score of ≥5) was used as the reference standard.[24]

Statistical Analyses

To determine the prevalence of AMS for establishing the pretest probability of AMS, a random-effects meta-regression was performed based on the reported prevalence of AMS as a function of altitude. The midpoint of the range of altitudes reported by study participants was used to assign an altitude for each study included in this analysis. A pooled analysis was performed that included all the data, then score-specific meta-regressions were performed to compare the relationship between the prevalence of AMS and altitude for the LLQS using various thresholds for establishing the presence of AMS (LLQS ≥3, LLQS ≥4, and LLQS ≥5): the AMS-C of 0.7 or greater (derived from the Environmental Symptoms Questionnaire III, see eAppendix 1 in the Supplement); the Hackett clinical score of 3 or greater; and the Chinese AMS score. In studies using the VAS(O) for AMS, differing thresholds (as defined in each article) were used to establish a diagnosis of AMS. Between-study variance was estimated using the I^2 statistic.[41] The proportion of between-study variance explained by altitude was estimated using the R^2 statistic.

The 3 instruments that could be compared with the LLQS were the AMS-C, the VAS(O), and the CFS. To obtain summary estimates of likelihood ratio (LR), sensitivity, and specificity with respective 95% CIs for each of the 3 instruments, a bivariable analysis for findings derived from more than 4 studies was used, and a univariable approach was used for studies in which there were fewer than 3 studies because of sparse data and lack of model convergence.[42]

Analyses were performed using the packages meta and metafor in the R software package (R Foundation), version 3.2.2; Stata (StataCorp), version 14.2; SAS (SAS Institute), version 9.2; and Comprehensive Meta-Analysis (BioStat), version 2.2.064.

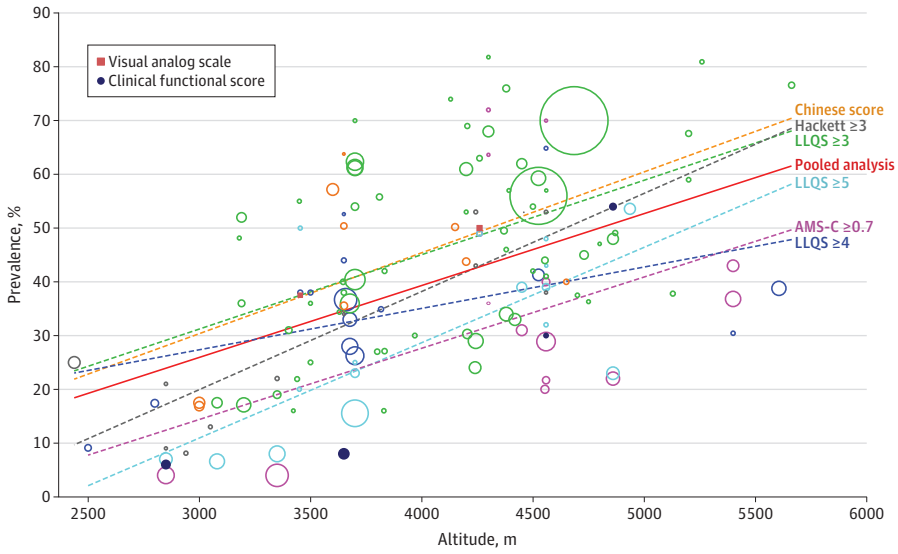
Results

The search yielded 1245 citations in the MEDLINE and EMBASE databases and 34 additional citations through manual screening of references (eFigure in the Supplement). After screening titles and abstracts, 838 abstracts were excluded (eFigure in the Supplement), and 407 full-text articles were assessed for eligibility (of which 305 were excluded because they focused on altitude-related disease other than AMS or because altitude data, the diagnostic instrument, or cutoff value used were not reported). Among the remaining 102 articles, 7 were excluded from the summary measures including 1 study that was limited to children aged 4 to 11 years at 1605 m (5300 ft) of altitude[43] and a study of teenagers hiking at low altitudes but not associated with mountain sickness.[44] The final selection comprised 91 articles (66 944 participants) for AMS prevalence (eTable 2 in the Supplement) using 6 different instruments: the AMS-C, Hackett clinical score, the LLQS, the Chinese AMS score, the VAS(O), and the CFS.

Prevalence of Acute Mountain Sickness

Random-effects meta-regression showed that studies conducted at higher altitudes reported a higher prevalence of AMS. Above 2500 m (8200 ft), for every 1000-m increase (3300-ft increase) in altitude, there was a 13% increase (95% CI, 9.5%-17%) in the

Figure. Random-Effects Meta-Regression of Prevalence of Acute Mountain Sickness According to Altitude



AMS-C indicates Acute Mountain Sickness-Cerebral score; LLQS, Lake Louise Questionnaire Score. The pooled analysis was stratified for each test: AMS-C (AMS-C of ≥0.7), the Hackett clinical score (≥3 points), the Chinese AMS score, and the LLQS at multiple cutoffs (LLQS ≥3, LLQS ≥4, LLQS ≥5). The data markers represent the size of each study. For indicative purpose, the few data points available for the instrument-in-comparison studies (visual analog scale score[45,46] and clinical functional score[22,47]), not included in the meta-regression, are also shown. Detailed results of pooled analyses are shown in Table 2.

Table 2. The Effect of Mean Altitude on Prevalence of Acute Mountain Sickness for Various Diagnostic Instruments, Assessed by Random-Effects Meta-Regression[a]

AMS Diagnosis Level	No. of Studies[b]	No. of Participants	Increase in AMS Prevalence per 1000 m, % (95% CI)	*P* Value	I^2, %	R^2, %
AMS-C ≥0.7	13	3206	13.3 (0.5 to 26.0)	.04	97	26
Hackett clinical score ≥3	6	4690	18.3 (10.9 to 25.6)	<.001	88	71
LLQS						
≥3	62	36 531	13.8 (7.4 to 20.2)	<.001	97	24
≥4	11	7551	7.7 (1.5 to 13.9)	.015	94	36
≥5	14	3186	17.8 (9.2 to 26.3)	<.001	93	58
Chinese AMS score	4	11 780	15.1 (−3.6 to 33.7)	.11	99	17
Pooled	**110**[c]	**66 944**	**13 (9.5 to 17)**	**<.001**	**98**	**28**

Abbreviations: AMS, acute mountain sickness; AMS-C, AMS-Cerebral score; LLQS, Lake Louise Questionnaire Score.

Conversion factor: To convert meters to feet, divide by 0.3048.

[a] Based on the random-effects meta-regression model of the 6 scores in 91 studies, the predicted prevalence (%) ≈ 13.4 × [altitude (m)/1000] − 21.5. For example, travelers at 2500 m would have an estimated prevalence of 12% ≈ 13.4 × [2500/1000] − 21.5.

[b] The number of studies was too low for meaningful meta-regression of the Hackett clinical score with a different cutoff (≥2; 4 studies[34,48-50]), the visual analog scale score (4 studies with only 2 allowing prevalence analysis[45,46]), the clinical functional score (2 studies[22,47]), and the LLQS (≥7 points; 1 study[51]).

[c] Some studies reported more than 1 instrument at a given altitude, explaining why the total number of studies for pooled analyses is greater than the number of included studies (91).

prevalence of AMS (**Figure**; **Table 2**). The majority of data was obtained from studies using the LLQS with a cutoff score of at least 3 to diagnose AMS. Despite the narrow CI, there was significant heterogeneity (I^2 = 98%) among these studies. The heterogeneity was partly explained (28%) by different altitudes examined in the studies. The contributions from other known determinants of AMS (such as speed of ascent, preacclimatization, and prophylaxis) could not be established because of insufficient detailed data on these factors.

Performance of Acute Mountain Sickness Diagnostic Instruments

Fourteen of the studies included head-to-head comparisons between at least 2 different AMS diagnostic instruments (1858 participants),[22,45-47,52-61] of which only 8 facilitated head-to-head comparative analysis used the LLQS score of 5 or greater as the reference standard (1344 participants)[22,45-47,52-55] (**Table 3**). Based on the QUADAS-2 tool assessing the quality of studies on diagnostic accuracy included in systematic reviews, these 8 studies had a low risk of bias and few applicability concerns (eTable 1 in the Supplement); therefore, they were used to pool summary estimates (**Table 4**).

Using an LLQS score of 5 or greater as the reference standard for establishing a diagnosis of AMS (Table 4), summary measures were as follows: for the VAS(O) (various thresholds): positive LR, 7.6; negative LR, 0.35; sensitivity, 69%; and specificity, 91%; for the AMS-C (score of ≥0.7 indicates AMS): positive LR, 8.2; negative LR, 0.36; sensitivity, 67%; and specificity, 92%; for the CFS (score of ≥2 indicates AMS): positive LR, 3.2; negative LR, 0.30; sensitivity, 82%; and specificity, 67%. When comparing these performances, no statistical differences were found for the comparison of positive LRs

Table 3. Major Characteristics of Publications Including Head-to-Head Comparisons Between Acute Mountain Sickness Diagnostic Instruments

Source (Location)	No. of Participants/ No. of Measurements	Women, %	Mean Age, y	BMI, Mean	Altitude, m	History of AMS	Prior Acclimatization	Speed of Ascent	Prophylaxis Allowed	Test Evaluated	Reference Standard
Comparative Analysis With the Reference Standard of LLQS ≥5[a]											
Maggiorini et al,[47] 1998 (Swiss Alps)[b]	Mountaineers, 490/490	19	37	20	2850-4559	NS	Partial	1-d ascent	NS	LLQS ≥4, LLQS ≥5, Hackett ≥3, AMS-C	LLQS ≥5
Dellasanta et al,[52] 2007 (Nepal)[c,d]	Trekkers, 266/1033	42	37	NS	3500-5400	NS	NS	2-5 d	Yes	CFS	LLQS ≥3, LLQS ≥4, LLQS ≥5, AMS-C ≥0.7
Kayser et al,[53] 2010 (Swiss Alps)[c,d]	Trekkers, 14/80	0	42	25	3647-4560	NS	No	>3 d	No	VAS(O), AMS-C	LLQS ≥3, LLQS ≥5
Van Roo, et al,[54] 2011 (Acacongua, Argentina)[e]	Mountaineers, 66/45	9.9	42	24.5	4365-6962	NS	NS	389m/d	Yes	VAS(O)	LLQS ≥5
Wagner et al,[45] 2012 (Orizaba, Mexico)	Mountaineers, 63/63	12	34	NS	4260-5640	NS	NS	>2 d	NS	VAS(O)	LLQS ≥5, AMS-C ≥0.7
Dehnert et al,[55] 2014 (Germany)[e,f]	Volunteers, 76/73	0	26.5	23.6	569-4500	NS	No	NS (simulated)	No	AMS-C	LLQS ≥3, LLQS ≥4, LLQS ≥5
McDevitt et al,[22] 2014 (Nepal)[c]	Trekkers, 337/337	51	35	23	2670-5400	NS	NS	>4 d	Yes, 44% using acetazolamide	CFS	LLQS ≥3, LLQS ≥5
Frühauf et al,[46] 2016 (Swiss Alps)	Volunteers, 32/32	60	38.8	22.7	3650	All	Partial	1-d ascent	NS	VAS	LLQS ≥5
Comparative Analysis Without the Reference Standard of LLQS ≥5[f]											
Savourey et al,[56] 1995 (France)[c,d,g]	Soldiers, 9/9	0	33	22.5	4500-5500	NS	None	9 h (simulated)[g]	Yes	LLQS ≥3	AMS-C ≥0.7, Hackett ≥3
Roeggla et al,[57] 1996 (Austria)	Mountaineers, 99/99	29	35.4	NS	2940	None	NS	1-d ascent	No	LLQS ≥3	Hackett ≥3
Hext et al,[58] 2011 (Chili)[d]	Volunteers, 23/138	26	42	NS	4392	NS	No	>3 d	NS	VAS(O)	LLQS ≥3, AMS-C ≥0.7
Slingo et al,[59] 2012 (Ladakh, India)	Volunteers, 28/1288	21	21	NS	3500-6000	NS	Yes	NS	NS	VAS(O)	LLQS ≥3, LLQS ≥5
Chen et al,[60] 2013 (China)	Soldiers, 339/339	1	1	22.4	3200	NS	No	>2 d	NS	Chinese AMS	LLQS ≥3
Subudhi et al,[61] 2014 (Chacaltaya, Bolivia)	Volunteers, 21/21	43	43	22.4	5260	NS	No	3 h (from 4000 m)	No	AMS-C	LLQS ≥3

Abbreviations: AMS-C, Acute Mountain Sickness-Cerebral score; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CFS, clinical functional score; LLQS, Lake Louise Questionnaire Score; NS, not specified; VAS(O), visual analog scale for the overall feeling of mountain sickness.

Conversion factor: To convert meters to feet, divide by 0.3048.

[a] These studies were used for the comparative analysis with the reference standard of LLQS ≥5 in Table 4.

[b] In the original study, the CFS was used as the reference standard. Because of detailed tables available in the publication, sensitivity-specificity 2 × 2 tables were able to be recalculated the using the LLQS ≥5 as the reference standard for the purpose of this analysis.

[c] Additional data were obtained from the authors and used for the calculations.

[d] The number of participants is less than the number of samples because of measurement of the same participants at multiple altitudes.

[e] The number of participants is greater than the number of samples because of incomplete data for some participants.

[f] These studies could not be included in the comparative analysis with LLQS ≥5 in Table 4 because of insufficient data to reconstruct the sensitivity-specificity 2 × 2 tables.

[g] Simulated ascent was performed in hypobaric or normobaric hypoxia laboratory conditions.

(χ^2_2 = 3.0; P = .22) and for the comparison of negative LRs (χ^2_2 = 1.4; P = .50). Among these 3 instruments, the heterogeneity was highest for the positive LR of the CFS, attributable to the study by Maggiorini et al,[47] which included the highest number of study participants (n = 490) and had a positive LR of 11, sensitivity of 77%, and specificity of 93% (Table 4).

Discussion

Seven different instruments (LLQS, AMS-C, VAS[O], VAS[C], Hackett clinical score, Chinese AMS score, and CFS) were found in the literature in which the diagnosis of AMS was described. For 5 of these

Table 4. Pooled Diagnostic Accuracy of Selected Instruments for Diagnosis of Acute Mountain Sickness Compared With the Lake Louise Questionnaire Score of 5 or Greater

Source by Instrument	No. of Participants	Prevalence of AMS, %	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
VAS(O)[a]						
Kayser et al,[53] 2010	80	18	79 (57-100)	92 (86-99)	10 (4.3-25)	0.23 (0.08-0.63)
Van Roo et al,[54] 2011	45	49	82 (66-98)	91 (80-100)	9.4 (2.5-36)	0.20 (0.08-0.49)
Wagner et al,[45] 2012[b]	63	49	65 (48-81)	97 (91-100)	21 (3.0-145)	0.37 (0.23-0.59)
Frühauf et al,[46] 2016	32	50	50 (26-74)	75 (54-96)	2.0 (0.8-5.3)	0.67 (0.38-0.17)
Summary measures[c]		38	69 (55-80)	91 (83-96)	7.6 (3.6-16) I^2 = 64%	0.35 (0.22-0.53) I^2 = 55%
AMS-C ≥0.7						
Dellasanta et al,[52] 2007	266[d]	43	63 (54-72)	93 (89-97)	9.6 (5.2-18)	0.39 (0.31-0.50)
Wagner et al,[45] 2012	56[e]	61	79 (66-93)	82 (66-98)	4.4 (1.8-11)	0.25 (0.13-0.50)
Dehnert et al,[55] 2014	73	42	77 (63-92)	95 (89-100)	16 (4.1-64)	0.24 (0.12-0.46)
McDevitt et al,[22] 2014[b]	3376	28	54 (44-64)	91 (87-95)	6.0 (3.8-9.3)	0.50 (0.40-0.63)
Summary measures[d]		37	67 (55-77)	92 (88-95)	8.2 (5.3-13) I^2 = 25%	0.36 (0.26-0.50) I^2 = 62%
CFS ≥2[f]						
Maggiorini et al,[47] 1998[g]	490	10	77 (64-89)	93 (91-95)	11 (7.5-16)	0.25 (0.15-0.42)
Dellasanta et al,[52] 2007	266[d]	39	82 (74-89)	53 (45-61)	1.7 (1.4-2.1)	0.34 (0.22-0.53)
McDevitt et al,[22] 2014	337	23	84 (76-93)	55 (49-61)	1.9 (1.6-2.2)	0.28 (0.17-0.48)
Summary measures[e]		21	82 (77-87)	67 (37-97)	3.2 (1.4-7.2) I^2 = 97%	0.30 (0.22-0.39) I^2 = 0%

Abbreviations: AMS, acute mountain sickness; AMS-C, Acute Mountain Sickness-Cerebral score; CFS, clinical functional score; LLQS, Lake Louise Questionnaire Score; LR, likelihood ratio; VAS(O), visual analog scale for the overall feeling of mountain sickness.

[a] The thresholds for VAS(O) were heterogeneous between the original studies: Kayser, 18%; Wagner, 16%; Van Roo, 35%; and Frühauf, 42%.

[b] Additional unpublished data were obtained from the authors and used for calculations.

[c] Random-effects bivariate meta-analyses were performed for sensitivity, specificity, and LRs.

[d] Prevalence analysis was made using the cohort of 266 participants, but sensitivity and specificity analyses were made using the sample of 1033 LLQS/AMS-C doublets.

[e] Separate random-effects univariate meta-analyses were performed for sensitivity, specificity, and LRs.

[f] CFS is sometimes rated from 1 to 3 rather than 0 to 3, but the clinical definition of AMS is always the same (symptoms leading to functional impairment) even if the threshold is sometimes 1 or greater rather than 2 or greater.

[g] Based on the detailed tables in the study, the sensitivity-specificity 2 × 2 tables were back-calculated using the LLQS ≥5 as the reference standard for the purpose of this analysis.

instruments (LLQS, AMS-C, Hackett clinical score, Chinese AMS score, and VAS[C]), AMS is determined by the presence of several neurological, gastrointestinal, and respiratory symptoms that develop at high altitude because there is no reliable biomedical test for diagnosis of AMS. The number of symptoms evaluated by these instruments varies as does the weighting for the severity of the symptoms. The remaining 2 instruments (VAS[O] and CFS) explore other aspects of AMS. The VAS(O) measures a patient's perception of being unwell from AMS. The CFS, which has the simplest scoring system, diagnoses AMS based on the extent of functional impairment of daily activities that might occur at high altitude. The LLQS can be considered the de facto reference standard for diagnosing AMS for both clinical and research purposes. Our study showed that even though the various instruments emphasize different aspects of AMS, the VAS(O), AMS-C, and CFS scores performed similarly for diagnosing AMS. The performance of the Hackett and Chinese AMS scores could not be assessed because of insufficient published data regarding their diagnostic accuracy.

The relationship between altitude and AMS was examined using random-effects meta-regression. Beginning at the altitude of 2500 m (8200 ft), the commonly accepted definition of high altitude for every 1000 m (3300 ft) of ascent, the prevalence of AMS increased by approximately 13%. Less than one-third (R^2 = 28%) of the relation between altitude and AMS prevalence was explained by altitude alone. This is likely because many well-recognized AMS risk factors such as previous episodes, speed of ascent, preacclimatization, and use of medical prophylaxis were not controlled for or were incompletely reported in most studies of AMS.

The AMS-C, the VAS(O), and the CFS had similar diagnostic accuracy for severe AMS when compared with the LLQS when its score threshold was greater than 5. These results were not entirely unexpected for the AMS-C because it was derived from the LLQS. The similar performance of the VAS(O) and the CFS instruments, compared with the AMS-C, was not anticipated. By assessing a nonspecific functional impairment induced by altitude exposure, independent of the presence and nature of the symptoms, the CFS and, in part, the VAS(O) explore different aspects of AMS than the other instruments.[35,58] Despite the differences in CFS and VAS(O) assessment, the performance of these simpler instruments was good and comparable to that of AMS-C. This observation is consistent with the new concept that AMS might not be a single entity but may manifest in different ways and present as symptom clusters that vary between patients (fatigue and insomnia vs headache and sleep disturbances vs headache alone).[62]

Determining which instrument might perform better at diagnosing AMS at different altitudes was challenging because the

instruments have not been compared directly with one another at the same altitudes. At higher altitudes, there is higher risk of AMS evolving to life-threatening high-altitude cerebral edema. In this situation, an instrument with greater sensitivity (such as the CFS) is preferred because it is important to identify cases of AMS even at the risk of overdiagnosis. At lower altitudes (for example, <4000 m [13 100 ft]), where risk of severe AMS is less, one might favor a more-specific instrument such as the AMS-C or VAS(O), which will facilitate the decision for the need of medical prophylaxis if a patient plans reascent to similar altitude.

In clinical settings, a simple diagnostic instrument such as the CFS may be adequate, but this may not be true for research studies. Because most research of AMS conducted during the last 2 decades used the LLQS and the AMS-C as reference standards for establishing a diagnosis of AMS, these 2 instruments remain the best to use for AMS research because newer studies can then be compared with older ones.

This systematic review highlights the need of a better definition of AMS based on current pathophysiological and clinical understanding. An ideal AMS diagnostic instrument should consider the variable expression of AMS symptoms and avoid conferring too much weight to a single symptom.[62] A longitudinal prospective study with repeated measurements of AMS symptoms, possibly with extra measurements such as arterial oxygen saturation,[63-65] is warranted and will be required to assess the predictive nature of AMS symptoms.

Limitations

In the absence of objective measures to diagnose AMS, the LLQS was used as a reference standard for establishing a diagnosis of AMS. The LLQS is not an ideal standard because it relies on the presence and severity of the patient's subjective symptoms. No study has used the rapid disappearance of altitude-related symptoms with descent as a reference standard. This approach would be less dependent on clinical judgment for establishing a diagnosis of AMS.

Because of insufficient granularity of AMS studies for the examination of the contribution of individual symptoms to AMS, it was not possible to determine the relative importance of each symptom in each scoring system. This analysis would be important for 2 reasons. First, AMS might not be a single entity. Rather, it might consist of symptom clusters (fatigue and insomnia vs headache and sleep disturbances vs headache alone) that affect individuals differently.[62] Second, controversy exists about the inclusion of headache as an essential symptom of AMS (required by the LLQS) and the equivalent weight given to disrupted sleep compared with the other 4 symptoms (headache, gastrointestinal upset, fatigue, and dizziness) in the LLQS.[66-68]

Some of the heterogeneity between studies observed when estimating the prevalence AMS at different altitudes might be explained by differences in the individual characteristics of included participants. The studies of AMS have frequently relied on convenience samples of unselected travelers at different study locations. Compared with studies at lower altitudes (<4000 m [13 100 ft]), observational field studies performed at very high altitude might include more experienced travelers who might be less susceptible to AMS. At these higher altitudes, generalization of our findings to trekkers and occasional climbers is uncertain.

The diagnostic instruments assessed in this review were not developed for use with children. The language used in the LLQS questions might require modification for use with children and the instrument validated in this population.[43,69] Headache, the cardinal symptom of the LLQS, is difficult to assess in children. Children and adolescents report AMS symptoms at low altitude, complicating the establishment of an AMS diagnosis.[43,44] Consequently, we excluded articles examining AMS in children or adolescents.

Conclusions

For the diagnosis of AMS, the VAS(O), AMS-C, and CFS display similar performances as the LLQS using a score of 5 or greater, but the number of comparisons was limited and not controlled for the presence of potential risk factors. A pragmatic choice in clinical settings is to use the CFS because of its simplicity. Travelers with no reduction or with mild reduction in daily activities should be reassured, whereas travelers with moderate or more reduction in their daily activities should use the LLQS with a score of 5 or greater in making the diagnosis of severe AMS requiring intervention.

Scenario Resolution

The clinical vignette depicts a typical presentation of altitude-related symptoms. Based on our model, predicted prevalence of moderate to severe AMS at 4000 m (13 100 ft) is approximately 33% (Figure). The presence of an important functional impairment (CFS = 2) from multiple symptoms in an otherwise healthy person increases the likelihood of that person having AMS (positive LR, 3.2). Thus, the probability that the patient has AMS is approximately 55%. An estimation of the AMS-C can be calculated from the symptoms listed in the introduction and would be approximately 1.4, which is twice the threshold value of 0.7.

The presence of symptoms recorded using the LLQS (fatigue, dizziness, and nausea) strengthens the likelihood of AMS. This scenario also highlights how a lack of reported headache would have excluded this diagnosis when using only the LLQS definition because headache is considered to be a cardinal symptom. This traveler, his companions, or both need to understand the potential risks of AMS (and high-altitude cerebral edema), as well as the importance of correct behavior and pharmacologic strategies to adopt when reexposing to similar or higher altitudes.

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