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Index Measured at an Intermediate Altitude to Predict Impending Acute Mountain Sickness

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ABSTRACT

MODESTI, P. A., S. RAPI, R. PANICCIA, G. BILO, M. REVERA, P. AGOSTONI, A. PIPERNO, G. E. CAMBI, A. ROGOLINO, A. BIGGERI, G. MANCIA, G. F. GENSINI, R. ABBATE, and G. PARATI. Index Measured at an Intermediate Altitude to Predict Impending Acute Mountain Sickness. *Med. Sci. Sports Exerc.*, Vol. 43, No. 10, pp. 1811–1818, 2011. **Purpose**: Acute mountain sickness (AMS) is a neurological disorder that may be unpredictably experienced by subjects ascending at a high altitude. The aim of the present study was to develop a predictive index, measured at an intermediate altitude, to predict the onset of AMS at a higher altitude. **Methods**: In the first part, 47 subjects were investigated and blood withdrawals were performed before ascent, at an intermediate altitude (3440 m), and after acute and chronic exposition to high altitude (Mount Everest Base Camp, 5400 m (MEBC1 and MEBC2)). Parameters independently associated to the Lake Louise scoring (LLS) system, including the self-reported and the clinical sections, and coefficients estimated from the model obtained through stepwise regression analysis were used to create a predictive index. The possibility of the index, measured after an overnight stay at intermediate altitude (Gnifetti hut, 3647 m), to predict AMS (defined as headache and LLS $\geq$ 4) at final altitude (Capanna Margherita, 4559 m), was then investigated in a prospective study performed on 44 subjects in the Italian Alps. **Results**: During the expedition to MEBC, oxygen saturation, hematocrit, day of expedition, and maximum velocity of clot formation were selected as independently associated with LLS and were included in the predictive index. In the Italian Alps, subjects with a predictive index value $\geq$ 5.92 at an intermediate altitude had an odds ratio of 8.1 (95% confidence limits = 1.7–38.6, sensitivity = 85%, specificity = 59%) for developing AMS within 48 h of reaching high altitude. **Conclusion**: In conclusion, a predictive index combining clinical and hematological parameters measured at an intermediate step on the way to the top may provide information on impending AMS.
Key Words: LAKE LOUISE SCORE, OXYGEN SATURATION, COAGULATION, THROMBOELASTOMETRY

Nowadays, owing to the modern tourist industry, access to high altitudes is made easy. Within 6–12 h after arrival at altitudes greater than 2500 m and consequent acute exposition to hypobaric hypoxia, nonacclimatized mountaineers may experience nonspecific symptoms including headache, nausea, anorexia, insomnia, fatigue/lassitude, vomiting, and dizziness (14). When these symptoms are assessed and rated in severity on a scale of 1–3 with the generally accepted Lake Louise scoring (LLS) system (22), the presence of acute mountain sickness (AMS) can be clinically diagnosed at the presence of a headache and at least one of the other symptoms.

Although not generally life-threatening, AMS is a clinical and pathophysiological continuum with high-altitude cerebral edema (14,25), a potentially fatal condition marked by the onset of ataxia and altered consciousness (2,14). As very few medications for AMS treatment are available, subjects with AMS should descend or be evacuated when LLS does not abate or worsen at any point within 24–48 h (25). At high altitude, this decision may, however, be hindered by accessibility of the hut, the geographic layout, and mostly by

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weather conditions. In addition, evacuation can sometimes be severely delayed among the local staff engaged in the expedition, who may deny AMS symptoms because they worry about losing their jobs (7). Therefore, a great interest exists regarding the possibility to screen subjects who may undergo a life threat (25).

Rate of ascent, heavy exercise, and individual susceptibility are the recognized important determinants for the onset of AMS (24). Individual susceptibility, however, can only be ascertained after a first episode (25), and although a relationship between oxygen saturation (SaO_2) and the subsequent development of AMS (9) was observed, at present there is no way to predict AMS (24). Mild to moderate AMS was found to be associated with different pathophysiological changes, including relative hypoventilation (20), impaired gas exchange (interstitial pulmonary edema) (13), fluid retention and redistribution (27), and increased sympathetic drive (5). Studies performed on mountaineers after a rapid ascent by foot to high altitude in the Alps (>4000 m) revealed that AMS with a score ≥ 4 was also associated with mild but significant shortening of activated partial thromboplastin time in the absence of any evidence of thrombin generation or fibrin formation (3); no blood coagulation changes were observed in mountaineers not reaching the same AMS score (4).

The complexity and the dynamic nature of AMS might represent significant obstacles toward the identification of a single parameter for predicting the disease. Therefore, the aim of the present study was to develop for the first time a predictive index, combining simple clinical and hematological parameters (i.e., hematocrit, oxygen saturation, etc.), which may be used at intermediate altitude to predict the onset of AMS at high altitude. A two-phase study was thus designed: in the first phase, we analyzed data collected within the frame of the HIGH altitude CArdiovascular REsearch (HIGHCARE) project at Mount Everest Base Camp (MEBC, 5400 m) to estimate the parameters to be included in the equation for deriving the clinical prediction index; in the second phase, an expedition to Monte Rosa (Italian Alps) was set up to validate the clinical prediction model by using data obtained after an overnight stay at the Gnifetti hut (3647 m) to predict an onset of AMS at the final high-altitude destination (Capanna Margherita (CM) hut, 4559 m).

MATERIALS AND METHODS

High-altitude ascent technique and laboratory setting. All volunteers were all in good general health and were all living permanently at <500 m above sea level. Exclusion criteria included subjects with known cardiovascular disease, chronic cardiovascular therapy, repeated prolonged exposures to altitudes > 3000 m in the 8 months preceding the expeditions, history of severe mountain sickness, history of angioedema, and pregnancy. Professional athletes were not included in the study. All subjects underwent a general safety medical checkup and baseline testing at the S. Luca Hospital in Milan (Italy) (baseline test). Both projects were approved by the ethical committee of the University of Milan Bicocca, and all subjects gave written informed consent to participate.

The first phase of the study was performed within the frame of the HIGHCARE project (2008), which included a total of 47 subjects (32 males and 15 females) age 24–62 yr (40 ± 9 yr). The expedition traveled from Kathmandu (1200 m) to Lukla (2800 m) by plane and on the same day by helicopter to Namche Bazaar (Namche, 3440 m), where we stopped off for measurements (September 14 and 15). Then, after a 2-d hike, we reached Periche (4200 m) where we stopped off again for 1 d for further acclimatization. Then finally after a further 2-d hike, we reached our destination (MEBC, 5400 m) where tests were carried out in a heated tent after acute (September 23–25, MEBC1) and prolonged exposure to high-altitude hypoxia (October 2 and 3; MEBC2; Fig. 1A). During the four evaluation sessions (sea level, exposure to intermediate altitude, acute and prolonged exposure to high altitude), all subjects underwent clinical evaluation with LLS assessment (22), transcutaneous hemoglobin oxygen saturation (pulse oximeter, Life

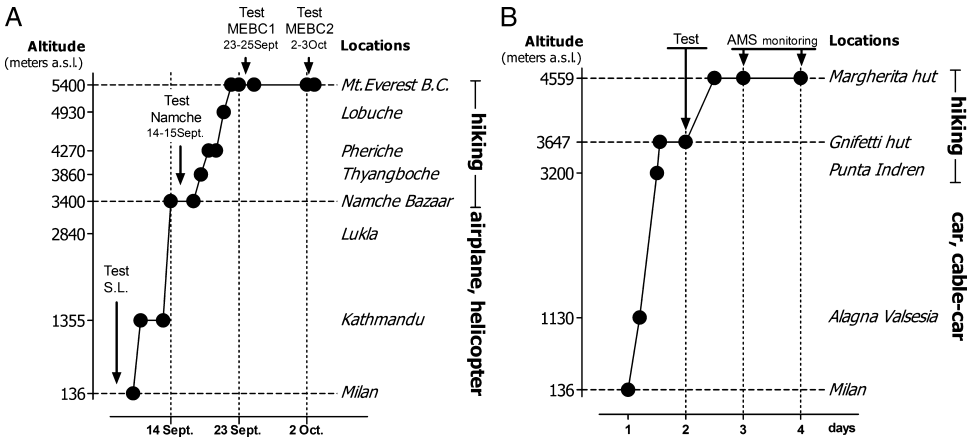

FIGURE 1—Altitude ascent profile of the expeditions to Mount Everest Base Camp (A) and CM (Monte Rosa) (B). Data collection points are indicated with *arrows*.

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Scope I; Nihon Kohden, Tokyo, Japan), and blood pressure (OMRON M5-I; Omron, Tokyo, Japan) measurements, and blood withdrawal.

The expedition to the CM hut, located on top of one of Monte Rosa's peaks, in the Swiss-Italian Alps, at an altitude of 4559 m, included a group of 44 subjects (23 males and 21 females) age 25–59 yr (36 ± 9 yr), 17 among them had also taken part in the HIGHCARE project. Two years elapsed between the Mount Everest Base Camp expedition and the trek to the CM, so there was sufficient washout between altitude exposures. Subjects traveled by car from Milan to Alagna Valsesia (1130 m), ascended by cable car up to Punta Indren (3200 m) and then reached by foot the Gnifetti hut (3647 m). After an overnight stay at the Gnifetti hut, all subjects underwent LLS assessment, pulse oximetry measurement, and blood withdrawal. Then, subjects hiked to CM, where LLS assessment was carried out 24 and 48 h after arrival (Fig. 1B).

AMS scoring system. To assess the degree of AMS, we used the self-reported and the clinical sections of the Lake Louise AMS scoring system (22). The AMS self-report is the sum of answers to five questions (headache, gastrointestinal symptoms, dizziness, lassitude or fatigue, sleeping difficulty), each one rating from 0 to 3. The clinical assessment score was given through the examination of three signs by the physician: mental status rating from 0 to 4, ataxia rating from 0 to 4, and peripheral edema rating from 0 to 2. The result of the clinical assessment score was added to the AMS self-report score. In our study, we defined AMS at the presence of headache with LLS ≥ 4. At CM, the highest LLS score recorded in the presence of headache was used to AMS. Subjects with AMS at the Gnifetti hut were not used in the evaluation of the predictive index.

Collection of blood samples. Venous blood samples for thromboelastometry (2.5 mL) were collected early morning, after overnight fasting, into a tube containing trisodium citrate 0.129 M at a proportion of 1:9 (anticoagulant–blood), and tests were started within 15 min after venipuncture. Hematocrit was immediately assessed by ABL77 (Radiometer Copenhagen, Bronshoj, Denmark). Venous blood samples for epinephrine (E) and norepinephrine (NE) assay (5 mL) were centrifuged, and the isolated plasma samples were snap-frozen and stored in liquid nitrogen until assay. NE and E levels were then assayed through high-performance liquid chromatography with electrochemical detection (21).

Thromboelastometry measurements. Intrinsic activation of hemostasis (INTEM assay) was triggered through cephalin (ellagic acid) in the four-channel ROTEM® device according to protocols and with type and concentration of reagents as provided by the manufacturer. Investigated parameters were the following: clotting time (CT), the time in seconds from the beginning of the coagulation analysis until an increase in amplitude of 2 mm; clot formation time (CFT), the time in seconds between an increase in amplitude of the thromboelastogram from 2 to 20 mm; maximum clot firmness (MCF), the maximal amplitude (mm) of the tracing reached in thromboelastogram; maximum velocity (MAXV), defined as the peak of the first derivative of the thromboelastographic clotting curve as expressed in millimeters per minute; alpha (α) angle, the tangent to the clotting curve through the 2-mm point (18). Intra-assay variation (based on four simultaneous measurements of two healthy male subjects) was 4% for CT, 10% for CFT, 4% for α angle, 4% for MCF, and 8% for MAXV. A preliminary test of instruments and experimental procedures was performed at simulated high altitude (21,000 ft, 6400 m) in the hypobaric chamber of the "Centro Sperimentale di Volo" (Air Force of Italy, Pratica di Mare, Rome, Italy). The exact same instruments were used in both expeditions.

Statistical analysis. Data collected in the HIGHCARE expedition are expressed as mean ± SD values or confidence limits (CL) at 95% for continuous variables. Categorical variables are presented as counts and percentages. Comparisons were made through ANOVA tests followed by *post hoc* ANOVA with Bonferroni test for multiple comparisons. Categorical variables were compared with Fisher's exact test.

Time patterns of variables measured in the subjects who did and did not experience AMS during the HIGHCARE expedition were compared using a linear mixed-effect model (group × time interaction fitted through the restricted maximum likelihood) (11). Variables independently associated with LLS were then selected through the stepwise multiple linear regression analysis (12), including data collected during all four steps of the HIGHCARE expedition (baseline, Namche, MEBC1, and MEBC2). In particular, age, gender, hematocrit, body mass index, systolic and diastolic blood pressure (BP), HR, breathing rate, day of expedition, barometric pressure, pulmonary artery pressure, oxygen saturation, catecholamine plasma concentration, and coagulation parameters were included as independent variables with LLS included as dependent variable. $P < 0.05$ was considered significant to stay into the final model. The regression coefficients with their 95% CL are presented with the P value of the t-test against 0.

The coefficients estimated from the model are the weight of each parameter. Therefore, each parameter was multiplied by its coefficient, and the results were summed to form a final combined value. The value was then expressed as the reciprocal multiplied by 100 so that a higher index may indicate a higher risk of developing AMS. Values measured at intermediate altitude (Namche) were then used to calculate the predictive index of each subject. Receiver operating characteristic (ROC) curve analysis was used to calculate the cutoff value and the sensitivity and specificity of the predictive index measured in Namche to predict AMS at MEBC1. A prospective study in the Italian Alps was then performed to avoid the bias of using the same classified observations used to estimate the parameters of the model (19).

In the second phase, the capability of the index measured at intermediate altitude (Gnifetti hut) to identify subjects

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with impending AMS at final altitude (CM) was then expressed as odds ratio (OR, calculated as the ratio of the odds of AMS occurring in the groups with index value below and over cutoff value). The following parameters of test performance were also calculated: positive predictive value (the proportion of patients with positive test results who had AMS at final altitude), negative predictive value (the proportion of patients with negative test results who had AMS at final altitude), sensitivity (the true positive tests per total affected patients tested), and specificity (the true negative tests per unaffected patients tested).

Data were analyzed using the Statistical Package for the Social Sciences (SPSS v17; SPSS, Inc., Chicago, IL).

RESULTS

Clinical findings and environmental variables during the HIGHCARE expedition. Mean atmospheric pressure and oxygen air pressure at the different step of HIGHCARE are reported in Table 1. Systolic and diastolic blood pressure significantly increased during the ascent, whereas O_2 saturation decreased (Table 1). At Namche, 24

TABLE 1. Variables measured at baseline, at Namche Bazaar (Namche), and Mount Everest Base Camp (MEBC1 and MEBC2) in the whole group ($n = 47$) and in subjects who experienced (AMS, $n = 16$) and who did not experience (No AMS, $n = 31$) acute mountain sickness (headache with LLS ≥ 4).

					ANOVA		Mixed Model Gr × t
Variables	**Baseline (Sea Level)**	**Namche (3300 m)**	**MEBC1 (5400 m)**	**MEBC2 (5400 m)**	***F***	***P***	***P***
Air pressure (mbar)	1016	679	534	538	—	—	—
O_2 air pressure (mbar)	213	142	112	113	—	—	—
O_2 saturation (%)	98 ± 1	91 ± 3[a]	78 ± 6[ab]	86 ± 4[abc]	233.66	<0.001	—
No AMS	98 ± 1	91 ± 3[a]	79 ± 6[ab]	87 ± 4[abc]	150.93	<0.001	—
AMS	98 ± 1	90 ± 3[a]	76 ± 5[ab]	85 ± 3[abc]	95.95	<0.001	0.412
Systolic BP (mm Hg)	118 ± 12	127 ± 17[a]	127 ± 14[a]	127 ± 14[a]	4.25	0.006	—
No AMS	120 ± 12	128 ± 18	127 ± 16	127 ± 16	2.12	0.101	—
AMS	115 ± 13	124 ± 16	128 ± 10[a]	128 ± 10	3.25	0.030	0.696
Diastolic BP (mm Hg)	75 ± 11	86 ± 9[a]	85 ± 9[a]	86 ± 8[a]	16.06	<0.001	—
No AMS	76 ± 11	87 ± 9[a]	85 ± 10[a]	85 ± 8[a]	8.74	<0.001	—
AMS	72 ± 10	84 ± 8[a]	86 ± 7[a]	87 ± 7[a]	9.00	<0.001	0.354
HR (beats·min^{-1})	61 ± 12	74 ± 13[a]	84 ± 16[ab]	78 ± 15[a]	15.51	<0.001	—
No AMS	58 ± 9	71 ± 12[a]	80 ± 15[ab]	75 ± 14[a]	15.19	<0.001	—
AMS	70 ± 16[d]	79 ± 15	91 ± 16[d]	83 ± 16	1.88	0.149	0.969
Breathing rate (breaths·min^{-1})	11 ± 2	12 ± 2	16 ± 4[ab]	14 ± 3[abc]	22.65	<0.001	—
No AMS	10 ± 2	11 ± 2	15 ± 4[ab]	13 ± 2[ab]	20.70	<0.001	—
AMS	12 ± 3[d]	13 ± 2[d]	17 ± 4[ab]	16 ± 3[d]	5.32	0.003	0.262
Pulmonary SP (mm Hg)	22 ± 3	27 ± 4[a]	35 ± 6[ab]	35 ± 6[ab]	62.24	<0.001	—
No AMS	23 ± 3	27 ± 4[a]	35 ± 6[ab]	35 ± 7[ab]	43.02	<0.001	—
AMS	21 ± 3	28 ± 4[a]	35 ± 5[ab]	35 ± 5[ab]	18.88	<0.001	0.414
Hematocrit (%)	46 ± 4	44 ± 5	49 ± 6[ab]	53 ± 6[abc]	30.14	<0.001	—
No AMS	46 ± 3	46 ± 5	51 ± 3[ab]	55 ± 4[abc]	40.43	<0.001	—
AMS	46 ± 5	40 ± 4[d]	46 ± 8[d]	50 ± 7[bd]	4.85	0.004	0.014
Epinephrine (pg·mL^{-1})	56 ± 33	42 ± 27	35 ± 18[a]	33 ± 27[a]	6.84	<0.001	—
No AMS	54 ± 30	46 ± 26	38 ± 17[a]	29 ± 26[a]	7.67	<0.001	—
AMS	56 ± 26	37 ± 30	30 ± 17	39 ± 29	0.89	0.454	0.039
Norepinephrine (pg·mL^{-1})	361 ± 188	583 ± 206[a]	986 ± 351[ab]	823 ± 631[ab]	22.62	<0.001	—
No AMS	374 ± 197	553 ± 179	976 ± 339[ab]	899 ± 643[ab]	15.33	<0.001	—
AMS	337 ± 175	642 ± 247	1005 ± 382[a]	680 ± 601[a]	7.06	<0.001	0.315
CT (s)	169 ± 20	193 ± 14[a]	204 ± 76[a]	183 ± 25	5.49	<0.001	—
No AMS	171 ± 24	194 ± 15	188 ± 64[a]	187 ± 26	5.04	0.003	—
AMS	165 ± 11	191 ± 11	175 ± 41	180 ± 24	2.31	0.089	0.928
CFT (s)	76 ± 18	91 ± 21[a]	88 ± 30[a]	85 ± 27	4.37	0.006	—
No AMS	81 ± 18	96 ± 22[a]	95 ± 30[a]	97 ± 27	3.72	0.014	—
AMS	65 ± 13[d]	82 ± 13[d]	73 ± 25[d]	75 ± 23[d]	1.79	0.162	0.284
MCF (mm)	61 ± 4	60 ± 4	62 ± 7	66 ± 8[abc]	6.15	<0.001	—
No AMS	60 ± 4	59 ± 4	61 ± 7	64 ± 10[b]	3.65	0.015	—
AMS	63 ± 3[d]	62 ± 3[d]	67 ± 6[d]	68 ± 4	3.53	0.022	0.176
α angle (°)	75 ± 4	72 ± 3[a]	72 ± 8[a]	73 ± 5	4.46	0.004	—
No AMS	74 ± 5	71 ± 4	70 ± 9[a]	71 ± 5	3.83	0.012	—
AMS	77 ± 2[d]	74 ± 3[d]	75 ± 5	75 ± 4	2.21	0.100	0.257
MAXV (mm·min^{-1})	18 ± 4	14 ± 3[a]	16 ± 5[a]	16 ± 4	7.26	<0.001	—
No AMS	17 ± 4	14 ± 3[a]	14 ± 3[a]	14 ± 3[a]	7.86	<0.001	—
AMS	20 ± 3	15 ± 3[ad]	19 ± 5[d]	18 ± 4[d]	3.30	0.029	0.014
LLS, *n*	0	1.09 ± 1.3[a]	2.65 ± 2.0[ab]	0.61 ± 1.0[c]	36.13	<0.001	—
0	47	23	7	29	—	—	—
1–3	0	22	25	16	—	—	—
4–6	0	2	13	1	—	—	—
>6	0	0	1	0	—	—	—

Continuous variables are expressed as mean ± SD.
[a] $P < 0.05$ versus baseline.
[b] $P < 0.05$ versus Namche.
[c] $P < 0.05$ versus MEBC1.
[d] $P < 0.05$ versus AMS at multiple comparison test.
BP, blood pressure; CFT, clot formation time; CT, clotting time; Gr × *t*, group-by-time interaction; MAXV, maximum velocity; MCF, maximum clot firmness; *n*, number of subject; SP, systolic pressure.

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TABLE 2. Multivariate modeling of LLS during the HIGHCARE expedition (stepwise multiple regression analysis).

Selected Variable	*B* Coefficient	95% CL	*P*
O_2 saturation (%)	−0.174	−0.21 to −0.14	0.000
Hematocrit (%)	−0.050	−0.09 to −0.01	0.027
Days (*n*)	−0.074	−0.12 to −0.03	0.002
MAXV (mm·min^{-1})	0.077	0.02 to 0.14	0.013

Variables included in the model: age, sex, body mass index, day of expedition, atmospheric pressure, CT, CFT, MCF, α angle, MAXV, hematocrit, systolic and diastolic pressure, HR, respiratory rate, pulmonary artery pressure, oxygen saturation, epinephrine and norepinephrine, with LLS as dependent variable.
Multiple $r = 0.714$.

subjects had symptoms of high-altitude sickness with an LLS > 0 (AMS in two subjects). When MEBC was reached (MEBC1), oxygen saturation showed a further reduction, with an increase in pulmonary artery pressure and respiratory rate versus the values measured in Namche ($P < 0.05$ for all; Table 1). At clinical check (MEBC1), 14 subjects had AMS (Table 1). After chronic adaptation (MEBC2), hemoglobin oxygen saturation increased, with significant reductions of respiratory rate, and only one subject had AMS (Table 1). Overall, during HIGHCARE expedition, 9 of the 15 women had AMS, whereas 7 of the 32 men had AMS ($P = 0.013$ at Fisher exact test between AMS in men and women).

Acute exposure to hypobaric hypoxia at Namche was associated with a significant increase of CT and CFT and reduction of α angle (Table 1). These changes were associated with a mild but significant increase of plasma norepinephrine (Table 1). At the MEBC1 step, a significant increase in hematocrit was detectable. At this step, INTEM assay confirmed the significant reduction of the intrinsic pathway activity observed at Namche, with norepinephrine plasma concentration showing a further increase versus Namche (Table 1).

Predictive modeling. Multivariate modeling through stepwise linear regression of the data collected from all participants in the HIGHCARE expedition identified four parameters independently associated with LLS (Table 2). In particular, a high velocity of clot formation (MAXV) increased the likelihood of high LLS (positive independent association with LLS), whereas oxygen saturation, hematocrit, and the duration of trekking at the time of assessment (days of expedition) decreased the likelihood of high LLS (negative independent association with LLS; Table 2).

The following algorithm was then created using the coefficients obtained for each selected variable:

$$\text{predictive index} = 1/[(0.174 \times \text{oxygen saturation (\%)}) + (0.050 \times \text{hematocrit (\%)}) + (0.074 \times \text{days}) - (0.077 \times \text{MAXV}(\text{mm·min}^{-1}))] \times 100$$

For example, for a patient who had reached intermediate altitude with 83% oxygen saturation, 43% hematocrit, on the first day of expedition, and with a MAXV of 16 mm·min^{-1}, a predictive index value of 6.48 can be calculated. Values measured in Namche were then entered into the algorithm to calculate the predictive index for each participant. Values ranged between 5 and 7. The predictive index measured in Namche had a sensitivity of 76.9% and specificity of 76.5% to predict AMS at MEBC1 for the cutoff value of 5.92 (Fig. 2). ROC analysis was also performed for oxygen saturation, hematocrit, and cutoff values (<91.5%, <43.5%, and >13.5 mm·min^{-1} respectively; Fig. 2).

Cox proportional-hazards stepwise regression was then used to analyze the effect of predictive index, hematocrit, oxygen saturation, and MAXV cutoff values on the occurrence of AMS (headache with LLS ≥ 4 at MEBC1). In particular, subjects with predictive index ≥ 5.92 in Namche had an OR of 5.4 (95% CL = 1.7–17.4, $P = 0.004$) of impending AMS.

2010 Monte Rosa research expedition. At the Gnifetti hut, seven subjects had AMS and were then excluded from further investigations. A predictive index value <5.92 was measured in 13 subjects; in this group, 10 subjects

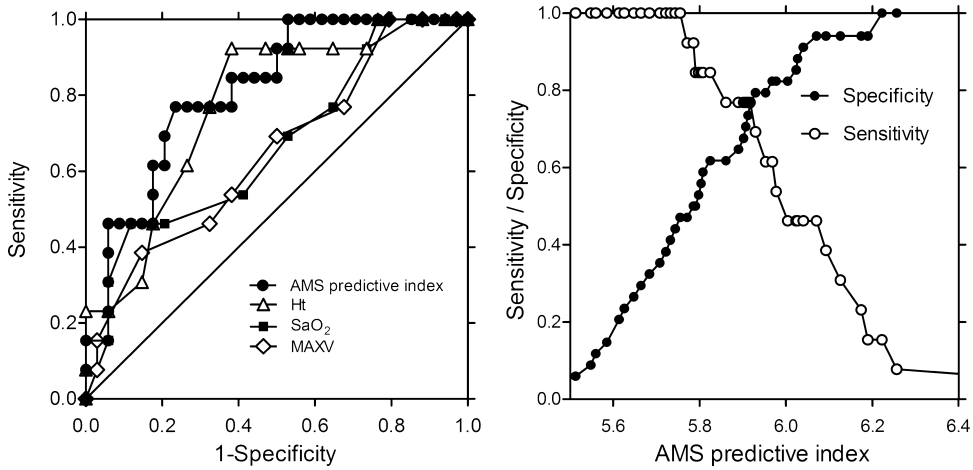

FIGURE 2—ROC curve of the sensitivity (true positives) versus 1 − specificity (false positives) of the AMS index, hematocrit, oxygen saturation, and MAXV in Namche Bazaar in predicting AMS (LLS ≥ 4) 24–48 h after arrival at Mount Everest Base Camp (MEBC1) (*left graph*). Sensitivity and specificity of AMS index (*right graph*).

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TABLE 3. Characteristics of subjects with predictive index values at the Gnifetti hut <5.92 or ≥5.92 and clinical assessment at 24 and 48 h after arrival at CM.

Location	Variables	Index < 5.92		Index ≥ 5.92		P
		n = 13		n = 24		
Gnifetti hut	O_2 saturation (%)	90.3 ± 1.6		87.2 ± 3.2		0.002
	Hematocrit (%)	51.1 ± 8.4		43.7 ± 6.0		0.004
	MAXV (mm·min^{-1})	14.3 ± 5.2		17.7 ± 4.5		0.045
	Predictive AMS index	5.8 ± 0.1		6.3 ± 0.3		—
CM	LLS, *n*	24 h	48 h	24 h	48 h	
	0	2	3	1	1	
	1–3	9	8	8	14	
	4–6	2	2	9	5	
	>6	0	0	6	3	
	AMS+	7		17		0.008[a]
	AMS−	10		3		

Continuous variables are expressed as mean ± SD.
[a] Two-tailed Fisher exact probability test.
AMS, acute mountain sickness (headache and LLS ≥ 4).

remained free from AMS at CM. Conversely, among the 24 subjects with a value of predictive index ≥ 5.92, 17 had AMS at CM ($P = 0.008$ at two-tailed Fisher exact test; sensitivity = 85%, specificity = 59%, positive predictive value = 71%, negative predictive value = 77%; Table 3). On the other hand, isolated assessments of oxygen saturation, hematocrit, and MAXV failed to predict the occurrence of AMS at CM (Fig. 3). Logistic regression selected the predictive index as the only predictor of AMS at CM (OR = 8.1, 95% CL = 1.7–38.6, $P = 0.009$), oxygen saturation, hematocrit, and MAXV being excluded from the model.

DISCUSSION

The present data reveal the new prospective to combine different variables measured at intermediate altitude on the way to the top in a single index able to predict the occurrence of AMS at high altitude. Expeditions to high altitude always consider intermediate steps where collection of simple data is feasible. In this setting, the addition of point-of-care instruments can screen mountaineers or local staff engaged in the expedition who may take advantage of waiting before continuing the trip.

The possible predictive value of oxygen saturation (SaO_2) and of the hypoxic ventilatory response was proposed to screen individual tolerance to hypoxia, but there is no scientific agreement whether these single tests are really useful

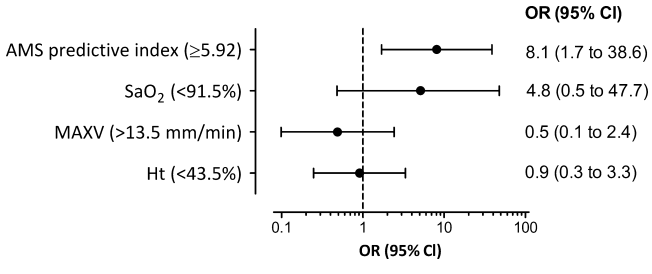

FIGURE 3—Univariate OR of developing AMS within 24–48 h after arrival at the CM hut (4559 m) for subjects with AMS index ≥6, oxygen saturation <91.5%, MAXV >13.5 mm·min^{-1}, and hematocrit <43.5% after an overnight stay at the Gnifetti hut (3647 m).

(10). The relationship to AMS susceptibility during the following expedition steps at high altitude (9,23), observed when SaO_2 was measured after prolonged exposure to hypoxia at altitude, indicates that the impairment of pulmonary exchange may occur before the onset of AMS clinical symptoms (17,28). When the time of exposure to hypoxia is short, SaO_2 changes markedly depend on the individual hypoxic ventilatory response (9). Studies investigating the hypoxic ventilator response in a hypobaric chamber failed, however, to show a consistent association with AMS (10). The inclusion in the model of other factors directly stimulated by hypoxia, such as blood lactate response, however, increased AMS prediction (10). AMS symptoms may then ensue as a secondary response, directly attributed to the reduced SaO_2, rather than simply occurring in conjunction with a declining SaO_2 value.

According to the current opinion, AMS is a mild form of high-altitude cerebral edema, both syndromes sharing a common pathophysiology linked by vasogenic edematous brain swelling that ultimately leads to intracranial hypertension (2,26). The change from aerobic to anaerobic glycolysis, occurring at values of arterial oxygen partial pressure (1), which can be reached in subjects exposed to high altitude (6,8), seems to play a role in the cytotoxic edema of subjects with hypoxia-induced AMS (26). The hypoxia-stimulated systemic accumulation of oxygen free radicals (2) may also have important implications for the vascular system by enhancing tissue factor at the transcriptional, as well as at the functional level, in endothelial cells (15). Previous studies performed at altitude revealed a mild activation of the intrinsic pathway of blood coagulation with a significant shortening of activated partial thromboplastin time linked to the increase of factor VIII procoagulant activity and von Willebrand factor antigen, in individuals with AMS (3,4). In addition to oxygen saturation, hematocrit value, and day of expedition, indeed multivariate analysis performed on our data selected the predictive value of the velocity of clot formation (MAXV) on activation of the intrinsic pathway.

The acute exposure to hypobaric hypoxia at Namche, which was reached very quickly because of the helicopter flight from Katmandu, was characterized by a longer time of

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clot formation (CT), a reduced velocity of clot formation (MAXV), and a significantly reduced α angle. Interestingly, the same depression of the intrinsic pathway of coagulation was still evident on arrival at MEBC1. At a further exploration of global data, multivariate stepwise analysis, however, selected a marker of coagulation activity (MAXV) as a positive independent predictor of LLS. The use of a simple point-of-care test such as thromboelastometry within the frame of a Himalayan expedition allowed us to overcome all logistic difficulties in performing a large battery of single coagulation tests. The correct transportation of blood samples to the central laboratory, a crucial point for all coagulation assays, might indeed represent an important source of bias in studies performed in the Himalayan region.

Altitudes ranging between 2300 and 4200 m were reported to be especially adequate for the determination of AMS susceptibility (9). Therefore, values measured in Namche (3400 m) of the four parameters selected as independent predictors of AMS (oxygen saturation, hematocrit, day of expedition, and MAXV) were used to build a predictive index for predicting AMS at MEBC (5400 m). Namche was reached by helicopter; thus, the possible confounding role of exercise was limited (24).

During the investigation in the Italian Alps, the predictive index test correctly identified individuals at risk for AMS in 85% of cases (sensitivity). The remaining 15% of people tested did not show the expected result for this test. For that 15%, the finding of a "normal" result can be misleading (false negative). A test's sensitivity is particularly important when searching to exclude a dangerous disease. In the present case, we decided to set the limit to a moderate value of LLS rather than attempt to screen more advanced stages of AMS. It might be difficult to make the subject understand and accept the possibility of having to wait before continuing the trip in the absence of AMS. However, it would be advisable to provide correct information of the possible onset of AMS in that single mountaineer, either for the subject itself or for the head of the expedition. On the other hand, the ability of the test to correctly exclude individuals who would not develop AMS (specificity) was 59%. Although unwarranted anxiety may be caused by the test in 41% of the subjects, the consequences of false positives are still minor at high altitude.

Cutoff values and predictive utility of SaO_2 measured at intermediate altitude >4200 m were indeed reported in studies with prospective field design (16,23). However, only information on negative predictive value (91%) is available for SaO_2 measured at 3500 m (16). Likewise, SaO_2 measured at the Gnifetti hut (3647 m) failed to predict impending AMS (Fig. 3). The integration of clinical and laboratory parameters in a single predictive index seems to be an advancement to investigate the complexity of AMS, although blood withdrawal may represent a main disadvantage of the strategy.

In conclusion, the present study explores for the first time the possibility to include different parameters, measured at intermediate altitude, in predictive index, to predict the onset of AMS at high altitude. The prospective study performed with this approach supports the possibility to screen recreational climbers who may gain advantage from waiting before continuing the trip, combining results from different point of care instruments. We propose that sensitivity (85%) and specificity (59%) of the predictive AMS index should stimulate further improvement by future studies, which might usefully explore a different combination of point of care tests, aimed at refining an optimal screening procedure that might be proposed for general implementation in huts at intermediate altitude, to reduce the risk of health problems in subjects on their way to high altitude targets.

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