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Using machine learning to determine the correlation between physiological and environmental parameters and the induction of acute mountain sickness



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From International Conference on Biomedical Engineering Innovation 2019 Kaohsiung, Taiwan. 15-19 November 2019

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Abstract

Background: Recent studies on acute mountain sickness (AMS) have used fixed-location and fixed-time measurements of environmental and physiological variable to determine the influence of AMS-associated factors in the human body. This study aims to measure, in real time, environmental conditions and physiological variables of participants in high-altitude regions to develop an AMS risk evaluation model to forecast prospective development of AMS so its onset can be prevented.

Results: Thirty-two participants were recruited, namely 25 men and 7 women, and they hiked from Cuifeng Mountain Forest Park parking lot (altitude: 2300 m) to Wuling (altitude: 3275 m). Regression and classification machine learning analyses were performed on physiological and environmental data, and Lake Louise Acute Mountain Sickness Scores (LLS) to establish an algorithm for AMS risk analysis. The individual R^2 coefficients of determination between the LLS and the measured altitude, ambient temperature, atmospheric pressure, relative humidity, climbing speed, heart rate, blood oxygen saturation (SpO₂), heart rate variability (HRV), were 0.1, 0.23, 0, 0.24, 0, 0.24, 0.27, and 0.35 respectively; incorporating all aforementioned variables, the R^2 coefficient is 0.62. The bagged trees classifier achieved favorable classification results, yielding a model sensitivity, specificity, accuracy, and area under receiver operating characteristic curve of 0.999, 0.994, 0.998, and 1, respectively.

Conclusion: The experiment results indicate the use of machine learning multivariate analysis have higher AMS prediction accuracies than analyses utilizing single varieties. The developed AMS evaluation model can serve as a reference for the future development of wearable devices capable of providing timely warnings of AMS risks to hikers.



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Keywords: Acute mountain sickness, Physiological information, Lake Louise acute mountain sickness score, Blood oxygen saturation, Heart rate variability, Multivariate analysis

Background

Acute mountain sickness (AMS) is a maladaptation syndrome that occurs at high altitudes [1, 2]. The occurrence rate of AMS in Taiwan is 36% [3], and patient age and AMS risk are not correlated [4]. An altitude of 2500 m is considered the threshold for AMS [5]. Mountain sickness is mainly caused by the low oxygen concentration in mountain environments. Low oxygen concentrations increase sympathetic nervous system activity and subsequently cerebral blood volume, resulting in hypoxia [6, 7]. Every year, millions of mountaineers engage in activities at high-altitude locations, with some overlooking and or dismissing the risk of AMS. Studies have revealed that AMS may cause life threatening conditions, including but not limited to high-altitude pulmonary and cerebral edema [1].

As of this writing, the mechanism and diagnosis of AMS remain uncertain. The 2018 Lake Louise Acute Mountain Sickness (LLS) is currently used to assess the severity of AMS. The score is based on headache, gastrointestinal symptoms, fatigue and/or weakness, and dizziness or lightheadedness. The maximum total score is 12 points, with 3-5, 6-9, and 10-12 points indicating mild, moderate, and severe levels of AMS, respectively [8]. However, because these scores are susceptible to subjective bias, an objective scoring system is necessary for diagnosing AMS symptoms. Multiple studies have indicated that in high-altitude environments, the human body stimulates the sympathetic and parasympathetic nervous systems to moderate the heart rate to adapt to the low-pressure and low-oxygen environment. This process of changing heart rate is observable in electrocardiograms (ECGs) [9-12]. Therefore, heart rate variability (HRV) is a critical factor in AMS diagnosis [13-17]. Relevant studies have proposed that AMS may be caused by multiple factors, including environmental conditions (e.g., altitude, ambient temperature, and atmospheric pressure) and biological factors (e.g., heart rate, blood oxygen saturation (SpO₂), and HRV) [2, 6, 18, 19]. Recent studies have used wearable devices to take physiological measurements; these studies measured users' heart rate, SpO2, and HRV to diagnose mountain sickness [20, 21].

The majority of studies on AMS perform linear analyses to build AMS prediction models with environmental and biological data (e.g., SpO₂ and HRV) that are collected daily. [13, 22, 23] As compared to linear analyses, multivariate analyses have higher model sensitivity, specificity, and accuracy; however, require increased quantities of data [24]. Therefore, to facilitate optimal training outcomes, multivariate analyses are performed on collected data in this study; and to ensure data is sufficient, environmental and physiological data are continuously and timely measured.

To summarize, this study employed machine learning algorithm applications to determine the correlation between AMS and environmental and physiological factors. The proposed algorithm can be used to predict the occurrence of AMS in real time. Furthermore, the algorithms can be applied to evaluate AMS risk among hikers, prevent the occurrence of hiking incidents, and ensure the safety of mountain activities.

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Results

Coefficient of determination (R2) analysis

We used linear regression analysis of the LLSs and the recorded altitude, ambient temperature, atmospheric pressure, relative humidity, climbing speed, heart rate, blood oxygen saturation (SpO₂), and heart rate variability (HRV) was performed using MATLAB R2020a to obtain the coefficient of determination (R^2) of each variable and all variables. The coefficients of determination for altitude, ambient temperature, atmospheric pressure, relative humidity, climbing speed, heart rate, SpO₂, HRV, and all variables were 0.1, 0.23, $1.2 \times 10^{-6} (\stackrel{.}{=} 0)$, 0.24, $1.5 \times 10^{-5} (\stackrel{.}{=} 0)$, 0.24, 0.27, 0.35, and 0.62, respectively. Single variable analysis revealed that HRV had the highest coefficient of determination, namely 0.35. The coefficient of determination for all eight variables was 0.62. The correlation analysis results are presented in Table 1. A comparison between the results of univariate and multivariate coefficient of determination analyses revealed that multivariate analysis yielded more satisfactory results. Therefore, this study employed the multivariate analysis results for subsequent binary classification analysis.

Binary classifier

Based on the suggestion of The Lake Louise AMS Score Consensus Committee in the 2018, we considered an LLS of 3–5 to indicate mild AMS [8]. Therefore, we set an LLS <3 as 0 and an LLS ≥3 as 1. The 25 machine learning algorithms employed the eight variables as the predictors to establish a machine learning model to diagnose mild AMS. The most favorable classification results were obtained by using bagged trees classifiers, achieving a sensitivity, specificity, accuracy, and area under the receiver operating characteristic curve (AUC) of 0.999, 0.994, 0.998, and 0.9999(≒1), respectively. See Table 2 for the classification results of each algorithm. Figure 1 shows the 4 algorithms: Fine Tree, Cubic SVM, Weighted KNN, Bagged Trees, which yielded the highest AUCs' respective receiver operating characteristic (ROC) curves.

Discussion

In the results show that using MATLAB R2020a line regression analysis and machine learning model to diagnose mild AMS. We use measured environmental and physiological factors to Coefficient of determination (R²) for LLS. And the binary classification method using bagged trees classifiers to obtain a high degree of accuracy modeling, a

Table 1 R-squared results for the linear regression model

Variable	Linear Regression R-Squared	р	
Altitude	0.1	< 0.001	
Ambient temperature	0.23	< 0.001	
Atmospheric pressure	1.2×10^{-6}	< 0.001	
Relative humidity	0.24	< 0.001	
Rise rate	1.5×10^{-5}	< 0.001	
Heart rate	0.24	< 0.001	
SpO ₂	0.27	< 0.001	
HRV	0.35	< 0.001	
Above all variables	0.62	< 0.001	

SpO₂: blood oxygen saturation. HRV: heart rate variability

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Table 2 Binary mild AMS classification results

Classifier type	Sensitivity	Specificity	Accuracy	AUC
Decision Trees				
Fine Tree	0.998	0.978	0.996	0.9999
Medium Tree	0.993	0.952	0.988	0.99
Coarse Tree	0.975	0.862	0.963	0.90
Discriminant Analysis				
Linear Discriminant	0.977 0.730		0.946	0.98
Quadratic Discriminant	0.997	0.707	0.952	0.99
Logistic Regression Classifiers				
Logistic Regression	0.978	0.858	0.965	0.99
Naive Bayes Classifiers				
Gaussian Naive Bayes	0.983	0.498	0.886	0.96
Kernel Naive Bayes	0.990	0.766	0.960	0.99
Support Vector Machines				
Linear SVM	0.981	0.858	0.967	0.99
Quadratic SVM	0.995	0.939	0.989	0.9999
Cubic SVM	0.997	0.967	0.994	0.9999
Fine Gaussian SVM	0.995	0.975	0.992	0.9999
Medium Gaussian SVM	0.995	0.914	0.985	0.9999
Coarse Gaussian SVM	0.974	0.895	0.966	0.98
Nearest Neighbor Classifiers				
Fine KNN	0.997	0.972	0.994	0.99
Medium KNN	0.996	0.957	0.991	0.9999
Coarse KNN	0.977	0.866	0.965	0.99
Cosine KNN	0.996	0.940	0.990	0.9999
Cubic KNN	0.995	0.949	0.990	0.9999
Weighted KNN	0.997	0.970	0.994	0.9999
Ensemble Classifiers				
Boosted Trees	0.998	0.984	0.997	0.9999
Bagged Trees	0.999	0.994	0.998	0.9999
Subspace Discriminant	0.970	0.795	0.951	0.97
Subspace KNN	0.997	0.959	0.993	0.9999
RUSBoosted Tree	0.999	0.929	0.991	0.9999

AUC: area under the receiver operating characteristic curve

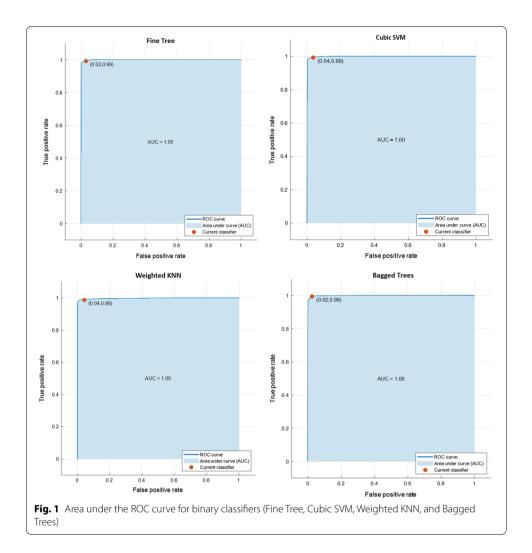
The Bagged Trees yielded the highest sensitivity, specificity, accuracy, and AUC; and was bolded for that reason

variety of factors in the machine learning to build models, can be conducive to the development of the AMS risk assessment model.

The results revealed that the participants' SpO_2 measured at the start of the path was lower than 94, relatively lower than their mean SpO_2 measured in their usual state at their home $(SpO_2: 97)$. In the experiment, the mean SpO_2 was approximately 83.5 (in Table 2), indicating the occurrence of anoxia [25]. A comparison between with previous studies [19, 26] demonstrates that with an increase in altitude, the atmospheric pressure decreased, thereby causing a decrease in oxygen tension and resulting in the participants experiencing anoxia [19]. Therefore, SpO_2 is a key indicator for diagnosing AMS.

Autonomic nervous system activity was monitored through HRV measurements; this method only requires observing R–R interval changes in the electrocardiogram (ECG). HRV are conducive to evaluating autonomic nervous system activity [9, 13, 14, 20] and

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produce fluctuations when the human body cannot adapt to low-pressure, low-oxygen environments; thereby indicating a decrease in the autonomic nervous system's responsiveness [27].

In the measured results, the participants' HRV significantly decreased in the mountain regions, thereby suggesting a correlation between the HRV-measured decrease in autonomic nervous system activity and anoxia severity, as indicated by SpO₂. In high-altitude environments with low pressure and low oxygen, the autonomic nervous system response of patients with AMS decreases. Decrease in HRV demonstrates to more suggestive of AMS symptoms than decrease in oxygen levels. During the on-site experiment, some participants experienced an increased heart rate and expressed discomfort.

Relevant studies on the factors that influence AMS have revealed a low correlation between heart rate and LLSs. During the hiking process, the participants' physiological indicators changed with hiking duration and altitude changes; in particular, participants experienced an increase in heart rate relative to their usual state.

The on-site experiment results indicate that in the hiking process, the variations of environmental factors resulted in changes in the participants' physiological

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factors. Additionally, a positive correlation was revealed between heart rate and LLSs, whereas SpO₂ and HRV exhibited a negative correlation with LLSs. This result is consistent with that of most studies on mountain sickness [9, 13, 20].

However, the coefficient of determination between atmospheric pressure and climbing speed with LLSs in this study was 0. Some studies have shown that the above two factors are related to AMS [9, 21]. This may be because this study only recorded data of participants engaging in hiking activities, and the elevation gain was slow; these two factors may have resulted in atmospheric pressure having a lower overall influence.

From the results, the 25 machine learning algorithms were employed to analyze the collected environmental and physiological factors, and demonstrated to yield sensitivity, specificity, and accuracy better than those of previous studies [13, 28], thus has comparatively higher developmental value.

Limitations

The experiment location was at an altitude over 2500 m, thereby meeting the threshold for acute mountain sickness (AMS). However, because no participant exceeded six hours of hiking, the recorded data are considered short-term measurements. Additionally, the data may have been influenced by underlying factors, including the amount of exercise the participant had performed in the previous day and their rest and sleep duration. Therefore, this study had inadequate data when compared with studies that collected data for three consecutive days [13, 26, 28, 29]. These factors may have contributed to the differences in the measured physiological values [19, 23, 26, 30]. Furthermore, the unfavorable coefficient of determination of atmospheric pressure in linear regression may have been caused by the short experiment duration, which prevented the collection of a comparatively high number data points.

After participants put on the wearable devices and hiked from the Cuifeng Mountain Forest Park parking lot to Wuling, the ECG pads may have loosened due to participant activity, resulting in data inaccuracies. During data processing, we eliminated data collected during incidences when recording equipment was loosened to increase data accuracy. However, this also reduced the number of data collected and may have resulted in error values. In future studies, we plan to use more secure physiological monitoring equipment to prevent the occurrence of errors.

Participants were predominantly male and were relatively old in age. In the future, we will recruit more woman participants ranging between 18 and 40 years old and increase the data collection instances along the planned hiking path to increase the AMS diagnosis accuracy.

The highest LLS recorded in this study was 7, thereby indicating moderate AMS (LLS range: 6–9 points). During the measurement, the participant expressed immense discomfort and an inability to continue hiking. In accordance with institutional review board regulations, participants had the right to stop hiking. Therefore, this study did not collect data on participants experiencing severe AMS (LSS range: 10–12). This study focused on diagnosing whether AMS occurred. In the future, we will more thoroughly research all levels of AMS severity.

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Conclusions

When traveling to mountain regions, the low-pressure and low-oxygen environment may result in the weakening of the human heart self-regulating function. This increases the possibility of AMS or other high-altitude conditions. The literature on AMS suggests that among hikers exposed to simulated atmospheric pressure or low-pressure and low-oxygen conditions, those with lower SpO_2 and HRV are more prone to experiencing AMS [31]. The analysis results of using environmental and physiological factors measured during on-site testing at over 2500 m altitude to predict AMS occurrence in participants revealed room for improvement.

We employed machine learning algorithms and various environmental and physiological factors for AMS diagnosis. Our model achieved a sensitivity and AUC of 0.99, indicating that the use of multivariate factors to train multivariate analysis-based machine learning models exhibit high developmental value in LLS evaluation. This machine learning algorithm can be coupled with equipment capable of the timely detection of multiple factor data to increase the accuracy for AMS predictions. Additionally, this application may prevent hikers from overlooking AMS symptoms and remind them to take preventive measures (e.g., taking medication or decreasing their altitude), thereby preventing the risk of severe AMS.

This study is the first to employ timely recorded environmental and physiological factors and multivariate analysis for AMS diagnosis. In terms of using LLS to diagnose AMS symptom severity, correlation analysis results revealed that the diagnosis effect of a single variable and LLS was unsatisfactory. However, the use of multiple variables and LLS exhibited satisfactory diagnosis effectiveness. The degree of correlation of ${\rm SpO_2}$ and HRV with AMS observed in this study was consistent with that of previous studies [32]. Additionally, correlation analysis results revealed that using more environmental and physiological factors with LLS may yield more satisfactory results. This finding is conducive to the establishment of AMS prediction and diagnosis models.

Methods

The pathogenesis and measurement methods of acute mountain sickness.

To research the physiological mechanisms of acute mountain sickness (AMS) [1, 2, 6], this study measured the environmental conditions (e.g., altitude, ambient temperature, atmospheric pressure, relative humidity, and climbing speed) and physiological variables (e.g., heart rate, blood oxygen saturation (SpO $_2$), and heart rate variability (HRV) in real-time. The Lake Louise Acute Mountain Sickness score (LLS) was adopted to evaluate AMS severity. The flowchart (Fig. 2) for pathogenesis and measurement methods of Acute Mountain Sickness.

Subjects

The experimental protocol was approved by the Tri-Service General Hospital Human Ethics Committee under registration number IRB: B202005136, and the informed consent of the experiment participants was obtained before this study. Adults between 25 and 55 years old capable of engaging in hiking activities and living below an altitude of 500 m were recruited as participants. Additionally, participants with diabetes,

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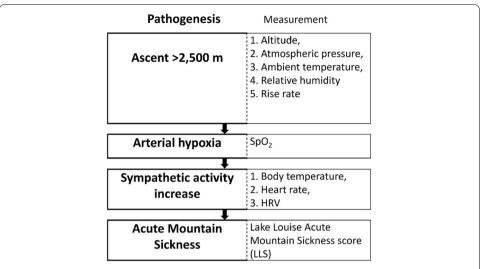


Fig. 2 The flowchart for pathogenesis and measurement methods of Acute Mountain Sickness. This figure simply illustrates the pathogenesis of acute mountain sickness. In mountainous areas over 2500 m above sea level, the human body responds to measurable physiological factors in order to adapt to the alpine hypoxia. The thick bordered boxes show acute mountain sickness pathogenesis, the thin bordered boxes are the respective method of measurement

neuropathy, cardiovascular and pulmonary diseases, or other symptoms that could influence heart rate variability (HRV) were excluded. Before testing, participants were required to administered the 2017 Physical Activity Readiness Questionnaire (2017PAR-Q+) [33] to confirm if any of the aforementioned diseases were present and whether the participants used drugs that may influence HRV, including plant-based neuromuscular-blocking drugs and sedative drugs.

Participant demographics

This study initially recruited 34 participants, however, only 32 fulfilled the inclusion criteria; two participants with self-reported cardiovascular disease and diabetes respectively were excluded. The final sample set were comprised of 25 men and 7 women. The mean participant age was 36.5 ± 8.1 years, and the mean body mass index (BMI) was 24.3 ± 2.36 . The mean home altitude of the participants was 65.4 ± 90.4 m. No participant had consumed drugs (e.g., acetazolamide) 30 days before the experiment. The most common acute mountain sickness (AMS) symptoms were weakness and dizziness, which were observed in 13 (40.6%) of the participants. The baseline demographics of the participants are listed in Table 3.

Physiological and environmental variable sensors and measurement methods

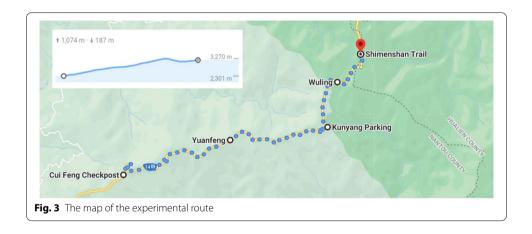
This study used the MD-670P Plus portable pulse oximeter and electrocardiogram (ECG) monitor (Department of Health Medical Device Manufacturing No. 001657, COMDEK Industrial Corp., Taiwan) to measure heart rate, blood oxygen saturation (SpO₂), and ECG. The monitor was connected to a Smart Link I application and a USB interface to transmit the data to a personal computer for data observation and analysis. Time domain analysis was performed on the collected ECG data, and the standard deviation of the R–R intervals was calculated to obtain the HRV data [15].

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Table 3 Baseline demographics

Demographic	Result
Age, y	36.5±8.1
Gender	
Male	25 (78%)
Female	7 (22%)
Body weight, kg	67.4±6.9
Body height, m	1.66 ± 0.07
BMI, kg/m ²	24.3 ± 2.36
Home altitude, m	65.4 ± 90.4
drug use within 30 day of ascent	
Acetazolamide	0(0%)
Steroids	0(0%)
Asthma medication	0(0%)
Pain reliever	0(0%)
Smoker	2(6.3%)
Alcohol consumer	0(0%)
History of AMS	5(15.6%)
Knowledge of AMS	14(43.8%)

Values are presented as mean \pm standard deviation. BMI body mass index



Additionally, the TI CC2650 SensorTag (Texas Instruments, Texas, USA) was employed to measure the environmental factors of a participant's position, including altitude, ambient temperature, atmospheric pressure, relative humidity, and climbing speed. Throughout the experiment, the participants were required to wear the pulse oximeter and ECG monitor and the SensorTag and hike along Provincial Highway 14. The participants embarked from the Cuifeng Mountain Forest Park parking lot in Nantou (2300 m altitude), passed the Yuanfeng Lookout (2756 m altitude), the Kunyuan parking lot (3085 m altitude), Wuling (3275 m altitude), and arrived at Shimen Mountain Class 3 Triangulation Point No. 6389 (3237 m altitude). The total hiking distance was 16.3 km, and the experiment duration was 8 h. The map of the experimental route is presented in Fig. 3 If the participants experienced swelling, itching, or

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other irritations where the wearable device was worn, they were required to immediately remove the device and were excluded from the experiment.

Participants' physiological variables

The participants' physiological variables were collected from the heart rate, SpO_2 , and ECG records of the portable pulse oximeter and ECG monitor. During the hiking activity, participants who experienced discomfort were immediately required to complete the online digital LLS. Additionally, professionals were assigned to the Cuifeng Checkpost, Yuanfeng, Kunyang parking, Wuling, and Shimenshan Trail to verbally administer the LLS to passing participants, thereby preventing the participants' subjective factors from influencing the acute mountain sickness assessment. The recording equipment automatically measured and recorded the data without requiring manual operation by the participants.

In the experimental process, data were not recorded during incidences when recording equipment (ECG pads and pulse oximeter) were loosened; a total of 8410 data points were collected and used for analysis. Table 4 presents the measured environment and participants' physiological variables. The average heart rate, ${\rm SpO_2}$, and HRV values of participants in mountainous areas were 115.84, 83.5, and 39.17, respectively; and were slightly lower than in their usual state. The measured physiological variables of the participants engaging in hiking activities were roughly equal to those recorded in previous studies [14–17].

Classification and evaluation

The MATLAB R2020a machine learning and deep learning tool (MathWorks, Natick, MA) [34] was employed for data analysis.

First, the linear regression model of regression learner applications was adopted to analyze the measured environmental and physiological factors. The coefficient of determination (\mathbb{R}^2) of each individual factor and all factors was calculated to determine factor correlations with the LLSs.

Subsequently, binary classification analysis was performed on the factors and the LLSs. The established mild AMS diagnosis model employed MATLAB R2020a's classification machine learning application that used the eight collected physiological and

Table 4 Environment and participants' physiological variables

	Altitude	Ambient temperature	Atmospheric pressure	Relative humidity	Rise rate	Heart rate	SpO ₂	HRV	LLS
Average	2868.79	24.26	698.11	0.64	3.08	115.84	83.5	39.17	0.64
Median	2852.89	24	693.36	0.67	3.96	117	84	38.9	0
Mode	3275	25	675.59	0.74	0	132	86	36	0
Std. Dev	297.59	1.73	18.9	0.12	3.4	19.32	4.92	10.76	1.3
Variance	88,562.6	3	357.16	0.01	11.6	373.14	24.18	115.71	1.7
Mini	2300	20	675.59	0.42	-10	77	70	13	0
Max	3275	29.4	742.2	0.78	10	160	94	80.5	7
Reliability (95%)	6.36	0.04	0.4	0.002	0.07	0.41	0.11	0.23	0.03

Std. Dev Standard Deviation

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environmental variables as predictors, and the classification output was set as whether a participant experienced mild AMS symptoms.

The classifier type selected in this study includes 25 machine learning algorithms such as: Decision Trees (Fine Tree, Medium Tree, Coarse Tree), Discriminant Analysis (Linear Discriminant, Quadratic Discriminant), Logistic Regression Classifiers (Logistic Regression), Naive Bayes Classifiers (Gaussian Naive Bayes, Kernel Naive Bayes), Support Vector Machines (Linear SVM, Quadratic SVM, Cubic SVM, Fine Gaussian SVM, Medium Gaussian SVM, Coarse Gaussian SVM) Nearest Neighbor Classifiers (Fine KNN, Medium KNN, Coarse KNN, Cosine KNN, Cubic KNN, Weighted KNN), Ensemble Classifiers (Boosted Trees, Bagged Trees, Subspace Discriminant, Subspace KNN, RUSBoosted Tree).

Finally, the characteristics of the developed AMS prediction model were evaluated based on sensitivity, specificity, accuracy, and area under the receiver operating characteristic curve (AUC). To prevent training and or testing bias, the 8410 data points were randomly divided into 90: 10 training and testing sets respectively. The aforementioned 25 machine learning algorithms were used to build the model, and were validated with the tenfold cross validation to prevent reliance on sample characteristics; and also to stabilize the final model.

Statistical analysis

After a classification algorithm has trained on data, we want to examine the performance of the algorithm on a specific test dataset. We assessed the predictive performance of our model using a range of common performance metrics: sensitivity, specificity, accuracy, and area under the curve (AUC), all of which range from 0 to 1 [35]. From Table 5, estimated sensitivity is the proportion of subjects with the condition of the true positives that are diseased. Estimated specificity is the proportion of subjects without the condition of true negatives that are diseased-free [36]. Accuracy is a commonly applied metric from the machine learning domain.

The three conventional evaluation indicators (sensitivity, specificity and accuracy) were calculated as follows.

```
Sensitivity = TP/(TP + FN).

Specificity = TN/(FP + TN).

Accuracy = (TP + TN)/(TP + FN + FP + TN).
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We can adjust different thresholds to get the true positive rate versus false positive rate (equivalently, sensitivity versus 1–specificity), by plotting a Receiver Operating Characteristic curve (ROC) to get the area under the curve (AUC) size, we can use the ROC curve to find the classifier that maximizes the classification accuracy, or to evaluate the performance of the classifier in high sensitivity and high specificity regions. We adopted

Table 5 Confusion matrix for binary classification

	Diseased	Diseased-free
Positive diagnostic test	True positives (TP)	False positives (FP)
Negative diagnostic test	False negatives (FN)	True negatives (TN)

Where TP = number of true positive events, FP = number of false positive events

 $TN = number\ of\ true\ negative\ events,\ FN = number\ of\ false\ negative\ events$

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tenfold cross-validation to obtain the mean values and standard deviations of these evaluation indicators to fairly compare their performance. In detail, the dataset is divided into ten approximately equal-sized sub-datasets, and the positive samples are divided equally in each sub-dataset.

Abbreviations

AMS: Acute mountain sickness; LLS: Lake Louise acute mountain sickness scores; SpO_2 : Blood oxygen saturation; HRV: Heart rate variability; ECG: Electrocardiogram; 2017PAR-Q+: The 2017 physical activity readiness questionnaire; BMI: Body mass index; SVM: Support vector machines; KNN: K-nearest neighbors; AUC: Area under the receiver operating characteristic curve; ROC: Respective receiver operating characteristic curve; TP: True positives; FP: False positives; FN: False negatives; TN: True negatives (TN).

Acknowledgements

We thank all individuals who participated in this study.

About this supplement

This article has been published as part of BMC Bioinformatics Volume 22 Supplement 5 2021: Proceedings of the International Conference on Biomedical Engineering Innovation (ICBEI) 2019-2020. The full contents of the supplement are available at https://bmcbioinformatics.biomedcentral.com/articles/supplements/volume-22-supplement-5.

Author contributions

CYW and PNC performed experiments. PNC, CYW, CWT and LCS wrote the manuscript. PNC, SSL, TWH and KFL provided the concept and experimental design of the study and reviewed the paper prior to submission. All authors discussed the results, analyzed the data, and commented on the manuscript. All authors have read and approved the final manuscript.

Funding

The design and part writing costs of the study are funded by the Ministry of Science and Technology, Taiwan (109-2625-M-016-001) and costs of collection, analysis and interpretation of data and part writing are funded by the Ministry of National Defense-Medical Affairs Bureau (MND-MAB-110-080). Publication costs are funded by authors.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Ethics approval and consent to participate

The experimental protocol was approved by the TSGH human ethics committee under registration number IRB: B202005136, and the informed consent of the experimental subjects were obtained before this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 24 May 2022 Accepted: 25 May 2022

Published online: 31 May 2022

References

- 1. Hackett PH, Roach RC. High-altitude illness. N Engl J Med. 2001;345(2):107–14.
- 2. Bartsch P, Swenson ER. Clinical practice: acute high-altitude illnesses. N Engl J Med. 2013;368(24):2294–302.
- Wang SH, Chen YC, Kao WF, Lin YJ, Chen JC, Chiu TF, Liu SW. Epidemiology of acute mountain sickness on Jade Mountain, Taiwan: an annual prospective observational study. High Alt Med Biol. 2010;11(1):43–9.
- 4. Wu Y, Zhang C, Chen Y, Luo YJ. Association between acute mountain sickness (AMS) and age: a meta-analysis. Mil Med Res. 2018;5(1):14.

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- 5. Lopez Jl, Holdridge A, Mendizabal JE. Altitude headache. Curr Pain Headache Rep. 2013;17(12):383.
- Wilkinson M, Kirk J. Extreme altitude and illness: How can medical sciences help us to achieve the Everest dream? Morecambe Bay. Med J. 2019;8(5):122–5.
- 7. Prince TS, Thurman J, Huebner K. Acute mountain sickness. In StatPearls [Internet]. Treasure Island, FL. 2021.
- 8. Roach RC, Hackett PH, Oelz O, Bärtsch P, Luks AM, MacInnis MJ, Baillie JK. The 2018 lake Louise acute mountain sickness score. High Alt Med Biol. 2018;19(1):4–6.
- Sutherland A, Freer J, Evans L, Dolci A, Crotti M, Macdonald JH. MEDEX 2015: heart rate variability predicts development of acute mountain sickness. High Alt Med Biol. 2017;18(3):199–208.
- Coustet B, Lhuissier FJ, Vincent R, Richalet JP. Electrocardiographic changes during exercise in acute hypoxia and susceptibility to severe high-altitude illnesses. Circulation. 2015;131(9):786–94.
- 11. Mikołajczak K, Czerwi´nska K, Pilecki W, Poreba R, Ga´c P, Poreba M. The impact of temporary stay at high altitude on the circulatory system. J Clin Med. 2021;10(8):1622.
- 12. Fiorenzano G, Papalia MA, Parravicini M, Rastelli V, Bigi R, Dottorini M. Prolonged ECG abnormalities in a subject with high altitude pulmonary edema (HAPE). J Sports Med Phys Fitness. 1997;37(4):292–6.
- Huang HH, Tseng CY, Fan JS, Yen DH, Kao WF, Chang SC, Kuo TBJ, Huang CI, Lee CH. Alternations of heart rate variability at lower altitude in the predication of trekkers with acute mountain sickness at high altitude. Clin J Sport Med. 2010;20:58–63.
- Mairer K, Wille M, Grander W, Burtscher M. Effects of exercise and hypoxia on heart rate variability and acute mountain sickness. Int J Sports Med. 2013;34(8):700–6.
- Mellor A, Bakker-Dyos J, O'Hara J, Woods DR, Holdsworth DA, Boos CJ. Smartphone-enabled heart rate variability and acute mountain sickness. Clin J Sport Med. 2017;28:76–81.
- Karinen HM, Uusitalo A, Vähä-Ypyä H, Kähönen M, Peltonen JE, Stein PK, Viik J, Tikkanen HO. Heart rate variability changes at 2400 m altitude predicts acute mountain sickness on further ascent at 3000–4300 m altitudes. Front Physiol. 2012;3:336.
- Boos CJ, Vincent E, Mellor A, O'Hara J, Newman C, Cruttenden R, Scott P, Cooke M, Matu J, Woods DR. The effect of sex on heart rate variability at high altitude. Med Sci Sports Exerc. 2017;49:2562–9.
- Song H, Ke T, Luo WJ, Chen JY. Non-high altitude methods for rapid screening of susceptibility to acute mountain sickness. BMC Public Health. 2013;13:902.
- 19. Luks AM, Swenson ER, Bartsch P. Acute high-altitude sickness. Eur Respir Rev. 2017;26(143):160096.
- 20. Boos CJ, Bye K, Sevier L, Bakker-Dyos J, Woods DR, Sullivan M, Quinlan T, Mellor A. High altitude affects nocturnal non-linear heart rate variability: PATCH-HA study. Front Physiol. 2018;9:390.
- Muza SR. Wearable physiological sensors and real-time algorithms for detection of acute mountain sickness. J Appl Physiol (1985). 2018;124(3):557–63.
- 22. Jouanin JC, Dussault C, Beers PV, Piérard C, Beaumont M. Short half-life hypnotics preserve physical fitness and altitude tolerance during military mountainous training. Mil Med. 2009;174(9):964–70.
- Beidleman BA, Tighiouart H, Schmid CH, Fulco CS, Muza SR. Predictive models of acute mountain sickness after rapid ascent to various altitudes. Med Sci Sports Exerc. 2013;45(4):792–800.
- 24. Samelson S. Machine learning: the absolute complete beginner's guide to learn and understand machine learning from beginners, intermediate, advanced, to expert concepts EBook: steven samelson: gateway. Amazon; 2019.
- Mathew TM, Sharma S. High altitude oxygenation. [Updated 2021 Apr 16]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539701/
- Cobb AB, Levett DZH, Mitchell K, Aveling W, Hurlbut D, Gilbert-Kawai E, Hennis PJ, Mythen MG, Grocott MPW, Martin DS. Physiological responses during ascent to high altitude and the incidence of acute mountain sickness. Physiol Rep. 2021;9(7): e14809.
- 27. Rovere MTL, Bigger JT, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. The Lancet. 1998;351(9101):478–84.
- 28. Koehle MS, Guenette JA, Warburton DE. Oximetry, heart rate variability, and the diagnosis of mild-to-moderate acute mountain sickness. Eur J Emerg Med. 2010;17(2):119–22.
- 29. Boos CJ, Bakker-Dyos J, Watchorn J, Woods DR, O'Hara JP, Macconnachie L, Mellor A. A comparison of two methods of heart rate variability assessment at high altitude. Clin Physiol Funct Imag. 2017;37(6):582–7.
- 30. Schneider M, Bernasch D, Weymann J, Holle R, Bartsch P. Acute mountain sickness: influence of susceptibility, preexposure, and ascent rate. Med Sci Sports Exerc. 2002;34(12):1886–91.
- 31. Schommer K, Hammer M, Hotz L, Menold E, Bartsch P, Berger MM. Exercise intensity typical of mountain climbing does not exacerbate acute mountain sickness in normobaric hypoxia. J Appl Physiol (1985). 2012;113(7):1068–74.
- 32. Chawla A, Tripathi KK. Objective criteria for diagnosing high altitude pulmonary edema in acclimatized patients at altitudes between 2700 m and 3500 m. Med J Armed Forces India. 2015;71(4):345–51.
- 33. Warburton DER, Jamnik VK, Bredin SSD, Shephard RJ, Gledhill N. The 2017 physical activity readiness questionnaire for everyone (PAR-Q+) and electronic physical activity readiness medical examination (ePARmed-X+). The Health Fitness J Canada. 2017;10(1):29–32.
- 34. Choose Classifier Options MATLAB & Simulink. https://www.mathworks.com/help/stats/choose-a-classifier.html. Accessed 14 June, 2021.
- 35. Jiang J, Liu X, Zhang K, Long E, Wang L, Li W, Liu L, Wang S, Zhu M, Cui J, Liu Z, Lin Z, Li X, Chen J, Cao Q, Li J, Wu X, Wang D, Wang J, Lin H. Automatic diagnosis of imbalanced ophthalmic images using a cost-sensitive deep convolutional neural network. Biomed Eng Online. 2017;16(1):132.
- 36. Buderer NM. Statistical methodology: I. Incorporating the prevalence of disease into the sample size calculation for sensitivity and specificity. Acad Emerg Med. 1996;3(9):895–900.

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