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A clinical decision rule to exclude central vertigo in the emergency department: A prospective, multicenter, observational study

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Abstract: To ensure good outcomes in patients presenting with vertigo, accurate prediction ruling out central vertigo is crucial during initial assessment. This study was conducted to develop a clinical decision rule (CDR) using objectively measurable predictors to exclude central vertigo, while maintaining 100% sensitivity. This was a multicenter, prospective, cohort study analyzing patients presenting to the emergency departments of six hospitals in Japan from April 2011 to March 2014. Eligible patients were 3,001 patients aged > 15 years. Patients were excluded if they presented with trauma, intoxication, heatstroke, anaphylaxis, or unconsciousness. The main outcome measure, definitive diagnosis of central vertigo, was based on confirmation of intracranial bleeding on head computed tomography (CT) or cerebral or cerebellar infarction or tumor on brain magnetic resonance imaging (MRI). Univariate analysis and multivariate recursive partitioning analysis were performed. A total of 1,938 patients were enrolled. Of 1,133 cases, 60 were diagnosed with central vertigo. The CDR diagnosed central vertigo if any of the following were present: headache or neck pain, vomiting, sBP > 150 mmHg, BS > 140 mg/dL, or LDH > 230 IU/L, providing sensitivity of 100% (95% CI 94.0–100%) and specificity of 21.2% (95% CI: 18.9–23.7%) to exclude central vertigo. The rule was validated in 805 eligible patients, of whom 87 had central vertigo, demonstrating sensitivity of 100% (95% CI: 95.8–100%) and specificity of 20.0% (95% CI: 17.4–22.9%). A highly sensitive CDR to exclude central vertigo was developed for patients presenting with vertigo to emergency departments. Further verification is needed to generalize this CDR.

Keywords: emergency department management, clinical research, common disease, decision making, dizziness

Introduction

Vertigo is a relatively frequent symptom, occurring in about 5% of emergency patients. Of these, about 3% are thought to have central vertigo, which is almost always due to cerebrovascular accidents involving the cerebellum or brainstem (*1,2*). Overlooking central vertigo may result in death, serious complications, or sequelae (*3*). Accurate detection is crucial in managing patients who present with vertigo to the emergency department (ED). Therefore, many studies have been conducted with the aim of not overlooking or picking up central vertigo. Almost all clinical decision rules can be used only when the presence or absence of neurological abnormal findings can be discriminated such as HINTS (head-impulse, nystagmus, test of skew) for acute vestibular syndrome which is becoming mainstream (*4-6*). Also in "Standard neurotherapy: Vertigo" published by the Japanese Society of Neurotherapy in 2020, the diagnosis of central vertigo or peripheral vertigo was based on the judgment of neurological findings, and there was a description that used many photographs and figures (*7*). Whereas the presence or absence of neurological findings is important, observations are greatly affected by the level of clinical skill of the attending medical staff. In fact, there is a report of meta-analysis that showed HINTS varied in accuracy when used by trained neurologists and by emergency physicians alone, and was not accurate enough to rule out stroke when used by emergency physicians alone (*4*).

Therefore, the development of clinical decision rules (CDRs) that provide high sensitivity for central vertigo

derived only from objective findings and tests without neurological findings that can be used by inexperienced physicians is very useful in the ED. However, there are few reports of predictors of central dizziness without neurological findings.

The present study was conducted as part of the Emergency Medicine, Registry Analysis, Learning and Diagnosis (EMERALD) project, aimed at minimizing life-threatening diseases being overlooked in EDs in Japan. The objective of this study was to develop a CDR, known as the EMERALD Vertigo Rule, using objectively measurable predictors to exclude central vertigo, while maintaining 100% sensitivity and offering as high a specificity as possible.

Materials and Methods

Study design

This multicenter, prospective, cohort study was conducted in the EDs of six general hospitals in Japan from April 2011 to March 2014. A total of 3,001 patients, aged > 15 years, presenting with a chief complaint of vertigo were considered for enrolment. Patients who presented with vertigo due to trauma, intoxication from drugs or alcohol, heatstroke, anaphylaxis, and those who were unconscious at the beginning of assessment were excluded.

All patient assessments were performed by residents supervised by staff physicians or attending emergency physicians. Physicians were oriented to the study and instructed to enter clinical findings at the time of assessment into data collection software specially developed by the EMERALD project on a smartphone device.

To minimize interobserver differences and observer biases, the focus was on objectively measurable data such as age, sex, heart rate, systolic blood pressure (sBP) and diastolic blood pressure (dBP), and temperature, which were defined as the first reading by the attending nursing staff. Data on symptoms that were clearly distinguishable as being present or absent and past medical history from the patient interview were gathered.

A variety of data from blood samples, such as blood sugar (BS), serum transaminase, serum lactate dehydrogenase (LDH), serum sodium, serum potassium, hemoglobin concentration, white blood cell (WBC) counts, and platelet counts were also collected, since these factors needed only a small amount of blood to measure. Only routine examination modalities applied to emergency patients in Japanese EDs were used, and all results were obtainable within 30 min.

All patient data were anonymized before being uploaded to the internet server *via* direct smartphone connection. Collected anonymized data were monitored and cleaned by the Joint Center for Researchers, Associates and Clinicians (JCRAC), an authorized center for quality management of data. The final dataset for analyses was provided by JCRAC.

The primary outcome, central vertigo, was defined as vertigo caused by cerebrovascular disease or tumor as detected by cranial computed tomography (CT) and/or brain magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA). These were interpreted by emergency physicians, specialist neurological staff (neurologist or neurosurgeon), and/or radiologists. All participating hospitals were equipped with 64-row multidetector row CT scanners and an MRI device either in or close to the ED. CT was available within 1 h at all times. If the results appeared negative on plain CT and the patient was still suffering from vertigo, emergency physicians or residents hospitalized the patients and consulted neurological staff regarding whether the patients could be discharged.

Brain MRI/MRA might not be immediately available for these patients, depending on the situation. If the neurological staff suggested the patient would not need hospitalization, but the patient was still suffering from vertigo, the patient was admitted for observation and possible further intervention, as appropriate. Discharged patients were evaluated by outpatient follow-up or telephone interview.

Data from the Center Hospital of the National Center for Global Health and Medicine (NCGM) were defined as the derivation dataset, and data from the other five hospitals as the validation dataset. Two groups were compared: the central vertigo group (CV group) and the non-central vertigo group (non-CV group), in whom vertigo was not due to central vertigo. Univariate analyses were used to determine the strength of the association between each possible predictor variable and the outcome variable.

To develop a CDR, previously established methodological standards were followed (*8*). First, categorical variables showing values of $p < 0.05$ on univariate analyses were selected. Then, continuous variables showing values of $p < 0.05$ on univariate analyses were selected as clinically important possible predictors. Cut-offs for the selected, objectively measurable predictors were determined by receiver-operating characteristic (ROC) curve analyses.

Continuous variables were converted into categorical variables by the cut-offs. Setting the presence (1) or absence (0) of central vertigo as the outcome variable, multivariate, recursive partitioning analysis was performed to develop rules using only the selected and converted categorical variables. Sensitivity and specificity were estimated for each rule. Because a CDR for a life-threatening event such as central vertigo requires sensitivity of 100% with a narrow confidence interval, the practical rule with the highest specificity was selected. The CDR was verified using the validation dataset to determine the internal stability of the rule, and the sensitivity and specificity were calculated.

The research ethics board at each participating hospital approved the study protocol, which was designed in accordance with the STROBE C statement for observational studies. All procedures followed in this study were in accordance with institutional guidelines. Informed consent was obtained from all patients.

Statistical analysis

Wilcoxon's rank-sum test was used for continuous variables, and Fisher's exact test was used for categorical variables and multivariate recursive partitioning analysis to develop the CDR. Statistical analyses were performed using JMP V.11.2.1 software (SAS Institute, Cary, NC, USA).

Clinical Trial Registration

UMIN-CTR Clinical Trial-URL: *http://www.umin.ac.jp/ctr/index.htm*. Unique ID issued by UMIN: UMIN000004864

Results

A total of 1,236 consecutive patients were enrolled as the derivation dataset, and 1,765 consecutive patients were enrolled as the validation dataset. In the derivation dataset, exclusion criteria applied to 49 patients, whereas primary outcomes for 54 patients could not be confirmed without follow-up evaluation or telephone interview. The study flow for the 1,133 eligible patients is shown in Figure 1A. In the validation dataset, 1,764 patients were enrolled, of whom 14 patients were excluded according to the exclusion criteria. In a further 930 patients, primary outcomes could not be confirmed without a follow-up evaluation or telephone interview, whereas 16 patients had missing principal data; thus, 805 patients were eligible (Figure 1B). There were 60 central vertigo patients in the derivation dataset and 87 in the validation dataset.

Table 1 shows the classification by the causative disease and the percentage of patients whose medical images were inspected in the CV group (n = 60) and the non-CV group (n = 1,073) from among the enrolled patients in the derivation dataset. Cerebellar infarction (n = 30; 50.0%), cerebellar hemorrhage (n = 7; 11.7%), and brainstem infarction (n = 7; 11.7%) were the top three diseases in the CV group, whereas most cases of peripheral vertigo (n = 558; 52.0%) occurred in the non-CV group. CT was performed in 100% of the CV group and 72.8% of the non-CV group. MRI was performed in 53.3% of the CV group and 11.2% of the non-CV group.

Three patients (5.0%) in the CV group and 890 patients (82.9%) in the non-CV group were discharged from the ED. One of the three patients was initially diagnosed with peripheral dizziness as an emergency

Table 1. Classification by causative pathology and percentage undergoing imaging investigation in the CV group (n = 60) and non-CV group (n = 1,073) in the derivation dataset

Causative pathology	CV group (n = 60)
Cerebellar infarction	30 (50.0%)
Cerebellar hemorrhage	7 (11.7%)
Brainstem infarction	7 (11.7%)
Brainstem hemorrhage	2 (3.3%)
Other cerebrovascular diseases	12 (20.0%)
Brain tumor	2 (3.3%)
Imaging investigation	
Head CT	60 (100.0%)
Brain MRI/MRA	32 (53.3%)
Causative pathology	non-CV group (n = 1,073)
Peripheral vertigo	558 (52.0%)
Psychiatric disorders	112 (10.4%)
Neuroregulatory disorders	58 (5.4%)
Dehydration / Infectious disease	39 (3.6%)
Anemia / Gastrointestinal bleeding	20 (1.9%)
Hypertensive emergency	16 (1.5%)
Cardiovascular disease	14 (1.3%)
Electrolyte abnormality	11 (1.0%)
Others	245 (22.8%)
Imaging investigation	
Head CT	781 (72.8%)
Brain MRI/MRA	120 (11.2%)

CV, central vertigo; CT, computed tomography; MRI/MRA, magnetic resonance imaging/magnetic resonance angiography.

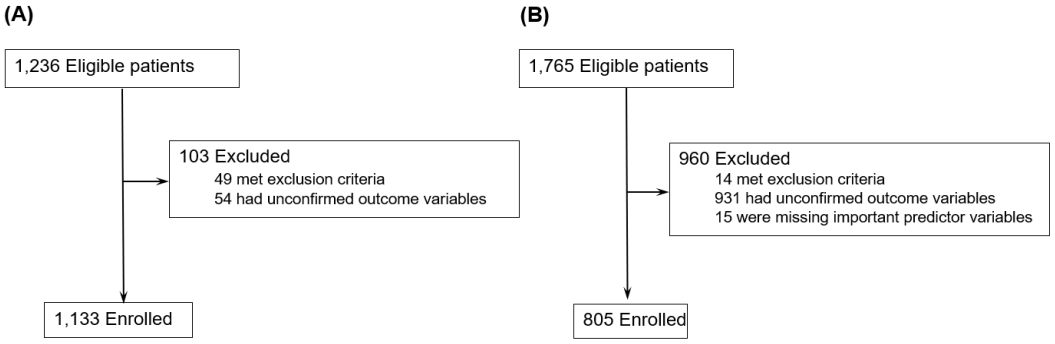

Figure 1. Flowchart of (A) the derivation dataset and (B) the validation dataset.

outpatient, but was finally diagnosed with central vertigo after consultation with an otolaryngologist. It was discovered via telephone interview that two patients, who did not undergo MRI or MRA, were initially diagnosed with peripheral vertigo and were discharged from EDs, but were then hospitalized elsewhere due to cerebellar infarction.

Table 2 shows the results of univariate analyses of the derivation dataset. The proportions of male patients and of patients with headache or neck pain and vomiting were significantly higher in the CV group than in the non-CV group. The proportion of patients with hypertension was significantly higher in the CV group, but there were no significant differences between the CV group and the non-CV group in the past medical or surgical history. Regarding vital signs and blood analyses, sBP, dBP, BS level, LDH level, and WBC count were higher in the CV group.

The cut-off values for continuous variables (sBP, dBP, BS level, LDH level, and WBC count) were determined using ROC curves. They were significantly higher in the CV group. Continuous variables were converted to categorical variables based on the cut-off value. These five converted variables and three categorical variables (including sex, vomiting, and headache and/or neck pain) were used for recursive partitioning.

As a result of the recursive partitioning analysis of the 1,133 enrolled patients, a CDR was developed using almost the same method as the EMERALD SAH rule (*9,10*), which is a CDR used to exclude the presence of subarachnoid hemorrhage in acute headache (Figure 2A).

Table 3 shows the comparison between the validation dataset of 718 eligible non-CV patients and the 945 excluded patients. In eligible patients, the median age was 69 years, and 36.8% were male, whereas in excluded patients, the median age was 68 years, and 36.5% were male. In addition, there were no significant differences in symptoms and measurable variables except for dBP and platelet counts between eligible non-CV patients and excluded patients.

The new CDR was verified with the validation dataset. Central vertigo was detected with sensitivity of 100% (95% CI: 95.8–100%) if the patient met any one of the following: presence of vomiting, headache or neck pain, sBP > 150 mmHg, BS > 140 mg/dL, or LDH > 230 IU/L. This CDR had a specificity of 20.0% (95% CI: 17.4– 22.9%) (Figure 2B).

As a result of the verification, the EMERALD

Table 2. Univariate correlations of variables with central vertigo

Characteristics	CV group (n = 60)	non-CV group (n = 1,073)	p value
Age (y)	65 (52–78)	63 (42–76)	0.07
Male sex	35 (58.3%)	446 (41.6%)	0.02
Symptom			
Headache or neck pain	19 (32.2%)*	197 (18.8%)*	0.02
Transient unconsciousness	1 (1.7%)*	59 (5.6%)*	0.37
Convulsions	0 (0.0%)*	7 (0.7%)*	1.00
Vomiting	36 (61.0%)*	392 (37.4%)*	< 0.01
Incontinence	1 (1.7%)*	7 (0.7%)*	0.36
Cochlear symptoms	4 (6.8%)*	146 (13.9%)*	0.17
Medical history			
Cerebral infarction	6 (10.0%)	69 (6.5%)*	0.29
Hypertension	32 (53.3%)	340 (32.2%)*	< 0.01
Dyslipidemia	7 (11.7%)	152 (14.7%)*	0.71
Diabetes mellitus	8 (13.3%)	105 (10.0%)*	0.38
Arrhythmia	3 (5.0%)	31 (3.0%)*	0.43
Neurological examination			
Cerebellar ataxia	19 (32.8%)*	18 (1.7%)*	< 0.01
Abnormal neurological findings	53 (89.8%)*	923 (92.0%)*	0.47
Vital signs			
Heart rate (bpm)	75 (67–87)	74 (66–84)	0.47
Systolic blood pressure (mmHg)	151 (137–180)	138 (119–160)	< 0.01
Diastolic blood pressure (mmHg)	87 (76–100)	76 (66–88)	< 0.01
Temperature (°C)	36.2 (35.8–36.7)	36.3 (36.0–36.7)	
Blood test results			
Blood sugar (mg/dL)	146 (118–175)	122 (104–146)	< 0.01
Serum lactate dehydrogenase (IU/L)	237 (203–267)	203 (178–239)	< 0.01
C-reactive protein (mg/dL)	0.08 (0.03–0.19)	0.06 (0.02–0.17)	0.10
Serum sodium (mEq/L)	139 (138–141)	140 (138–141)	0.28
Serum potassium (mEq/L)	3.8 (3.5–4)	3.8 (3.5–4)	0.98
White blood cell count (/μL)	7,900 (6,600–10,600)	6,900 (5,500–8,500)	< 0.01
Hemoglobin (g/dL)	14.1 (12.9–5.5)	13.6 (12.7–14.8)	0.07
Platelet count ($\times 10^4$/μL)	22.6 (18.9–26.9)	21.3 (17.7–25.4)	0.29

Continuous variables are indicated by medians (quartiles), nominal variables are indicated by numbers (proportion). CV, central vertigo. *: Percentages were calculated excluding those with missing data.

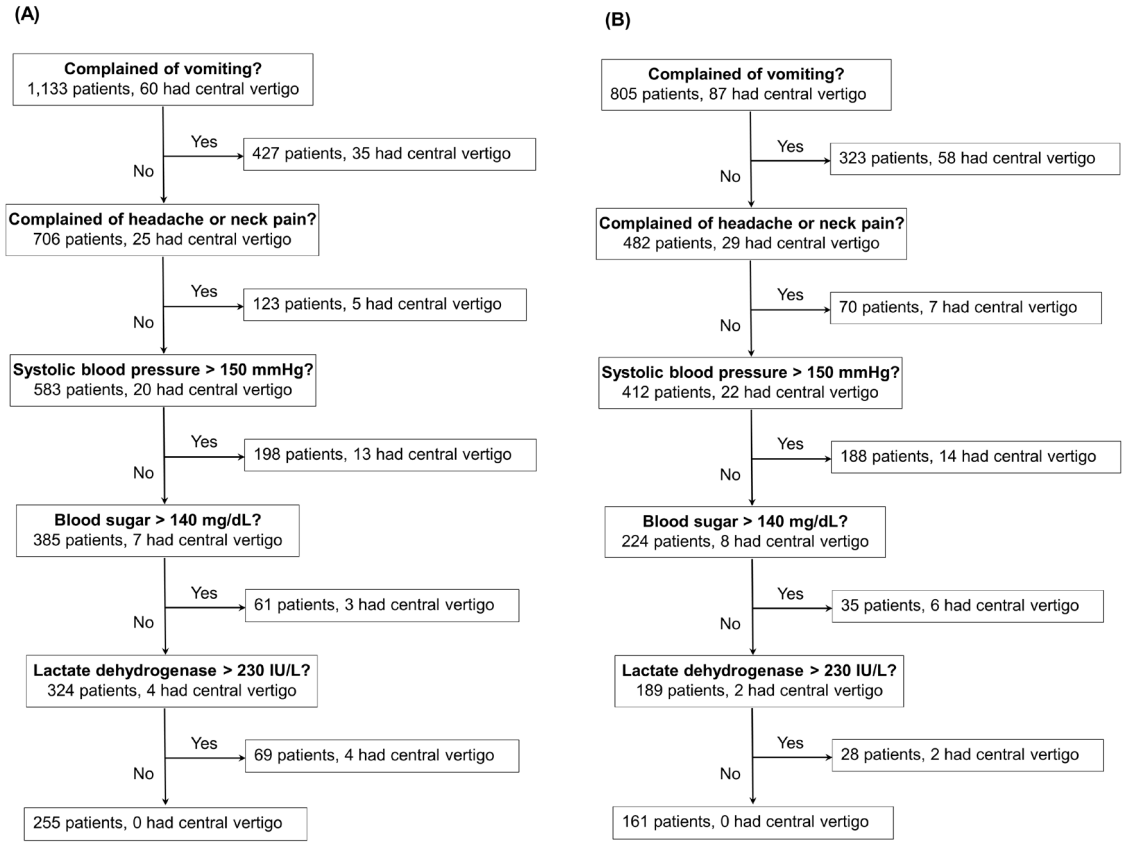

Figure 2. (A) A clinical decision rule excluding central vertigo with 100% sensitivity created using recursive partitioning, (B) Results of validation data using the created clinical decision rule.

Table 3. Comparison between validation data of 718 eligible non-CV patients and 945 excluded patients

Characteristics	Eligible non-CV patients (n = 718)	Excluded patients (n = 945)	p value
Age (y)	69 (58–77)	68 (57–76)	0.18
Male sex	264 (36.8%)	345 (36.5%)	0.75
Symptom			
Headache or neck pain	111 (15.5%)	168 (17.8%)	0.26
Transient unconsciousness	8 (1.1%)	21 (2.2%)	0.13
Convulsion	2 (0.3%)	7 (0.7%)	0.32
Vomiting	264 (36.8%)	396 (41.9%)	0.08
Incontinence	3 (0.4%)	3 (0.3%)	0.70
Cochlear symptoms	130 (18.1%)	147 (15.6%)	0.08
Medical history			
Cerebral infarction	65 (9.1%)	85 (9.0%)	0.86
Hypertension	288 (40.1%)	383 (40.5%)	1.00
Dyslipidemia	127 (17.7%)	80 (8.5%)	< 0.01
Diabetes mellitus	100 (13.9%)	107 (11.3%)	0.08
Arrhythmia	54 (7.5%)	111 (11.7%)	< 0.01
Neurological examination			
Cerebellar ataxia	24 (3.3%)	21 (2.2%)	0.21
Abnormal neurological findings	548 (76.3%)	599 (63.4%)	1.00
Vital signs			
Heart rate (bpm)	74 (66–86)	74 (65–83)	0.11
Systolic blood pressure (mmHg)	147 (128–67)	146 (128–164)	0.21
Diastolic blood pressure (mmHg)	82 (71–95)	80 (69–91)	< 0.01
Temperature (°C)	36.4 (36.0–36.7)	36.3 (35.9–36.6)	0.19
Blood test results			
Blood sugar (mg/dL)	126 (108–155)	132 (110–155)	0.10
Serum lactate dehydrogenase (IU/L)	214 (188–250)	214 (187–253)	0.67
C-reactive protein (mg/dL)	0.1 (0.04–0.2)	0.07 (0.03–0.17)	0.12
Serum sodium (mEq/L)	139 (138–141)	139 (138–141)	0.50
Serum potassium (mEq/L)	3.9 (3.6–4.2)	3.8 (3.6–4.2)	0.31
White blood cell count (/μL)	6,900 (5,400–8,600)	6,800 (5,400–8,400)	0.43
Hemoglobin (g/dL)	13.5 (12.6–14.4)	13.4 (12.3–14.3)	0.10
Platelet count ($\times 10^4$/μL)	20.7 (17.0–24.0)	21.9 (18.3–25.9)	< 0.01

Continuous variables are indicated by medians (quartile), nominal variables are indicated by numbers (proportion). CV, central vertigo.

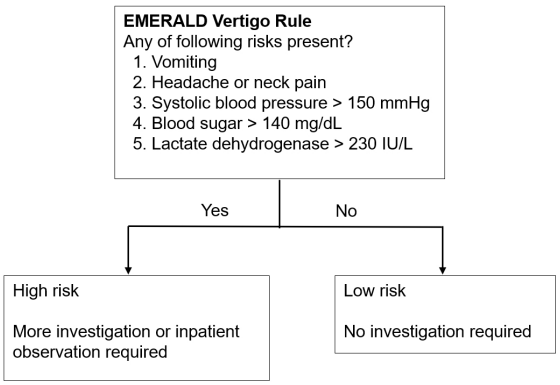

Figure 3. A proposed decision-making process for excluding central vertigo in vertigo patients.

Vertigo Rule was formulated as follows: in the presence of any of vomiting, headache or neck pain, sBP > 150 mmHg, BS > 140 mg/dL, or LDH > 230 IU/L, there is a possibility of central vertigo, and further examination or inpatient observation is warranted (Figure 3).

Discussion

Central vertigo may be overlooked in the initial management of vertigo patients in EDs. In EDs, many inexperienced residents are involved in patient management, and the reason for overlooking central vertigo was that the findings of these residents were likely less accurate and reproducible than those of neurological experts.

Kerber *et al.* reported that cerebrovascular disease was diagnosed in 3.2% (53/1,666) of patients presenting with vertigo. These patients were slightly older and more likely to be male than those without cerebrovascular disease (69.3 ± 11.7 *vs*. 65.3 ± 12.9 years, $p = 0.02$; 55% *vs*. 36% male, $p < 0.01$; respectively) (*2*) The present derivation dataset was compared with that of the report by Kerber *et al.* The percentage of central vertigo patients in the present study was significantly higher than the percentage in the report by Kerber *et al.* (5.6% *vs*. 3.2%, $p < 0.01$); however, the proportion of men in the non-CV group was consistent with their report. The age of patients tended to be higher in the CV group than in the non-CV group, but not significantly higher.

In the present study, the EMERALD Vertigo Rule was developed, with central vertigo suspected if any of the following five are present: vomiting, headache or neck pain, sBP > 150 mmHg, BS > 140 mg/dL, or LDH > 230 IU/L. It is not surprising that sBP and BS increase as stress increases, as in cerebrovascular disease, but the serum LDH value seems to be hardly related to stress. Prior to the 1990s, there were many reports that enzymes such as LDH in serum or cerebrospinal fluid increase significantly in stroke patients (*11-13*). These reports support LDH being one of the predictors used in the EMERALD Vertigo Rule.

The new CDR has 100% sensitivity to exclude central vertigo. Besides this, it was also ensured that the criteria were objectively measurable values that were easy to use during medical examinations in EDs. The sensitivity based on the validation dataset was also shown to be 100%; thus, the EMERALD Vertigo Rule seems to have a certain degree of external validity.

Despite being a prospective study, there were several deficits in the data. Simultaneous gathering of clean data proved difficult while emergency patient care was being provided. Some telephone numbers obtained were incorrect, and some patients did not have access to a telephone. Moreover, selection biases were likely given the large number of samples excluded. Missing validation data in 930 patients meant that primary outcomes could not be confirmed without follow-up evaluation or telephone interview, whereas 16 patients had missing principal data.

A total of 946 patients in whom primary outcomes could not be confirmed were those who were not diagnosed as having central vertigo during their initial medical examination in the EDs.

There were no significant differences in patients' characteristics, except dyslipidemia, arrhythmia, dBP, and platelet counts, between eligible non-CV and excluded patients (Table 3). Of the four significant characteristics (dyslipidemia, arrhythmia, dBP and platelet counts), the dBP, which was likely to be associated with the five parameters of the EMERALD Vertigo Rule, was significantly lower in the excluded patients than in the eligible non-CV patients. Since dBP was significantly higher in the CV group than in the non-CV group in the derivation data, a significantly lower dBP in excluded patients than in eligible non-CV patients did not increase the likelihood of including CV patients in excluded patients. It was not possible to directly prove that there were no patients with central vertigo among the excluded patients, but at least there were no relevant significant differences in the eligible non-CV patients and the excluded patients.

A meta-analysis by Robert Ohle *et al.* reported that HINTS when used by emergency physicians alone was not accurate enough to rule out stroke (*4*). Also, there are several reports that noted the need for training of emergency physicians to improve the accuracy of neurologic findings (*4,6*). In addition, we emphasized high sensitivity over low specificity, because ED care is focused on ruling out overt disease rather than making a definitive assessment. Although the EMERALD Vertigo Rule has less specificity, the focus was on creating more practical CDRs for inexperienced physicians who work extensively after-hours. This CDR seems to be very useful in practical clinical settings, because the rule is simple, and the predictors were shown to be not very subject to interobserver disagreement. Because the number of patients who undergo after-hours medical examinations continues to increase, it is also

quite useful that "only" about 20% of patients do not have to undergo detailed examinations and specialist consultations.

In conclusion, we propose that, when treating vertigo patients, further tests and follow-up inpatient observations are needed in patients who meet any of the following criteria: presence of vomiting, headache, or neck pain, sBP over 150 mmHg, BS over 140 g/dL, or LDH over 230 IU/L. The EMERALD Vertigo Rule may be useful in the initial management of emergency patients presenting with vertigo. Further validation will be required for its generalization.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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