Research Square

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Circadian variations in occurrence and the clinical presentation of Vestibular Migraine: A retrospective study

Wei Liu
First Affiliated Hospital of Soochow University
Le Yang
Fujian Medical University
Hongli Dong
Nanjing University of Chinese Medicine
Huifeng Qian
Nanjing University of Chinese Medicine
Hongru Zhao
First Affiliated Hospital of Soochow University
Yi Yang (13656229395@163.com)
First Affiliated Hospital of Soochow University
Wanli Dong
First Affiliated Hospital of Soochow University

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Abstract

Background: As a new clinical disease entity, vestibular migraine (VM) is considered to be the commonest cause of spontaneous episodic vertigo. This study is trying to explore the circadian variations in occurrence and the clinical presentation of VM.

Methods: We conducted a retrospective study and identified female patients who fulfilled the 2012 International Headache Society-Bárány Society Criteria for VM. Population's clinical data were collected, including onset time and descriptions of sensations experienced by our patients during VM attacks.

Results: A total of 189 female VM patients were included in our study. 74.0% of attacks in VM were presented in morning hours before 12 o'clock and the peak of occurrence was at about 7 o'clock. The attack frequency reached the baseline during 12:00-23:59 while there were two abnormal upward fluctuations at about 14:00 and 20:00. The biological circadian cycles may have greater impact of VM than lack of sleep. In addition, clinical presentations of vestibular symptoms including orthostatic vertigo, visually induced vertigo and dizziness showed variations among four 6-hour quadrants per day.

Conclusions: Occurrence as well as clinical presentations of vestibular symptoms exhibited circadian variations among VM patients. These data suggested that chronobiological mechanisms may play a role in vestibular migraine pathophysiology.

Introduction

As the most common neurologic cause of episodic vertigo, vestibular migraine (VM) is a variant of migraine resulting in vestibular symptoms in addition to migraine(1, 2). Despite a prevalence of between 1% and 2.7% of adult population(3), diagnosis of VM is challenging perhaps due to the broad spectrum of its manifestations, complex temporal patterns and its very recent nosological definition(4, 5). Several biological phenomena and diseases have specific circadian rhythms(6-8). The relatively high occurrence of migraine or benign paroxysmal positional vertigo attacks have been widely documented upon awakening in recently studies(9, 10). We also noticed that a lot of VM patients experienced sudden vertigo with or without severe headache during the morning hours in our clinic practice.

Therefore, we hypothesized that the occurrence and the presentation of VM may vary during different circadian periods. We conducted a review of VM patients of two hospitals to assess circadian variations in occurrence and the clinical presentations of vestibular symptoms.

Methods

Study Population

We conducted a retrospective review of patients at the neurology outpatient clinics of the First Affiliated Hospital of Soochow University and Suzhou TCM Hospital Affiliated to Nanjing University of Chinese

Medicine. A total of 197 female patients who fulfilled the 2012 International Headache Society-Bárány Society Criteria (included in the third version of the International Classification of Headache Disorder (ICHD-3)) for VM or probable VM were followed up by three months(11-13). The diagnoses were made by two senior neurologists and one senior otolaryngologist.

The exclusion criteria were as follows: (1) headache or vestibular symptoms attributed to secondary causes; (2) other causes of vestibular attack such as benign paroxysmal positional vertigo, Meniere's disease or transient ischemic attack of posterior circulation; (3) users of oral contraceptives or migraine prophylactic; (4) history of alcohol or drugs abuse; (5) history of head trauma or intracranial infection; (6) history of otorhinolaryngology surgery; (7) shift work.

Clinical information collection

We reviewed all study population's data: age, race, job, history of caffeine and alcohol, age of onset, relevant medical history, relevant family history, the onset time of this attack, symptoms experienced during this attack, self-reported triggers for this attack, neuro-otologic examinations, and clinical balance tests. All the descriptions of sensations experienced (vestibular symptoms and accompanied symptoms) by our patients during VM attacks were recorded and classified according the definitions of the Committee for Classification of Vestibular Disorders of the Bárány Society in 2012 and "Classification of Vestibular Symptoms" of the Bárány Society in 2009(11, 14). All patients gave informed consent and more detailed methods are available from the corresponding author upon reasonable request.

Statistical Analyses

We analyzed circadian variations in distribution of VM onset and clinical presentations by comparing them among four 6-hour quadrants per day: 00:00-05:59, 06:00-11:59, 12:00-17:59, 18:00-23:59.

Continuous variables were analyzed as mean and standard deviation or the median and interquartile range while categorical variables were analyzed as frequency and percentage, properly. Differences among these variables were assessed by the chi-square test or ANOVA. Post hoc analysis was performed with Bonferroni correction. Data analysis were presented using kernel density, radar plots and 100% stacked bar. The level of significance for these descriptive comparisons was established at 0.05 for two-sided hypothesis testing. Statistical analysis was performed in SPSS 25.0.

Result

Demographics and medical history

After 3-month follow-up, we identified 189 female VM patients according to the inclusion and exclusion criteria. Demographics and relevant medical history were showed in Table 1. The age was 42.0 (35.0, 52.0) years old; the duration of illness was 4.0 (1.0, 8.0) years. As a well-recognized comorbidity in migraine, 63.5% sufferers experience motion sickness, more than previous studies. 71 patients (37.6%) reported a family history of similar episodic vestibular symptoms (lasting from 5 minutes to a few days).

Occurrence

The circadian variation in VM occurrence is summarized in Table 2 and Figure 1. Among four 6-hour quadrants, VM attacks occurred most frequently during 06:00-11:59, followed by 00:00-05:59 and reached the baseline during 12:00-23:59 (Table 2). The peak of occurrence was at about 7 o'clock in the morning, and there were two abnormal upward fluctuations at 14:00 and 20:00.(Figure 1)

Clinical presentation

For all 189 attacks, activities at onset were classified into moving, rising, sitting and sleeping. Rising (36.5%) was presented most frequently and sitting (10.1%) was presented least. Even most attacks presented during the sleeping time, activities of moving their head around (moving and rising) were more relevant to provoking VM attacks (60.8% VS 29.2%) (Table 2).

We analyzed circadian variations in clinical presentation of VM by comparing them among four 6-hour quadrants per day: 00:00-05:59, 06:00-11:59, 12:00-17:59, 18:00-23:59 (Table 2). The radar plots in Figure 2 summarizes these data.

Most our patients experienced at least one vestibular symptom during attacks of VM. Spontaneous vertigo was the predominant vestibular symptom (42.3%) and it’s frequencies did not significantly differ among four 6-hour quadrants after adjustment. Dizziness was the second most frequent category of vestibular complaints (29.1%) and reported more frequently during 12:00-17:59, followed by 18:00-23:59. Orthostatic vertigo (22.8%) was most frequent during 06:00-17:59 and least frequent during 12:00-17:59. Frequencies of head motion induced vertigo (21.7%) also showed no significant difference among four quadrants and only 9 of our patients (4.8%) reported visually induced vestibular symptom. (Table 2)

During VM attacks, the majority experienced nausea and vomiting (59.8%), photophobia (58.7%) and phonophobia (55.0%). Headaches accompanied VM in only 34.9% of patients. Ictal aural symptoms like tinnitus were not common (13.2%) and just a few patients experienced visual aura (4.8%) (Table 2). The frequencies of all these accompanying symptoms showed no significant differences among four 6-hour quadrants per day (Table 2).

Self-reported triggers

Sleep deprivation was frequently reported as a trigger for VM attacks. Figure 4 shows the distribution of attacks (n=189) among four 6-hour quadrants per day, and sleep-related triggers was considered the precipitating factor. The percentage of sleep deprivation was shown in the Figure 3, and there was no significant difference among four quadrants.

Discussion

The key findings in our study are as follows: (1) 74.0% of attacks in VM were presented in morning hours before 12 o’clock; occurrence of VM peaked in the morning hours between 07:00-07:59, and reached

valley between 21:00-21:59; (2) clinical presentations of vestibular symptoms showed variations among four 6-hour quadrants per day; (3) attacks may be influenced by poor sleep, however, the biological circadian cycles may have greater impact of VM than lack of sleep. To our knowledge, this study was the first time to analyze the circadian variations in the occurrence and the clinical presentation of VM.

In our population, the age of onset was 36.00 (29.50, 44.00) years old, consistent other studies(15). But few of our patients had a personal history of alcohol or caffeine, that may due to the gender or local dietary habit and may affect the composition of influence factors.

For all attacks, frequencies of activities at onset differed among four 6-hour quadrants and “rising” (36.5%) was presented most frequently. The onset patterns of vestibular symptoms in each quadrant was related to the regular activity patterns of our population. But on the whole, vestibular symptoms were more often triggered by activities of moving their heads, which perhaps was one trigger unique to VM but not migraine headache(4). The attack of VM presented more frequently between 00:00-12:00 and reached its peak about 7 o'clock in the morning. This finding is similar to previous chronobiological studies that reported an increased frequency of morning headache attacks among migraineurs(16). We also found abnormal upward fluctuations at 14:00 and 20:00, which may correlate to the taking of food and suggesting a role of the sympathetic nervous system(17).

In addition, most of our VM patients experienced more than one accompanying symptom and vestibular symptom. Orthostatic vertigo was reported more frequent in the morning hours while dizziness was reported more frequent in the afternoon hours. Headaches may or may not accompany vestibular symptoms during VM attacks, consistent with previous study(5). The majority reported nausea with or without vomiting, photophobia or phonophobia. Just a few of our patients described tinnitus and visual aura, which is much lower than those data reported in other studies(4, 18).

Through these analyses, we can get a preliminary conclusion about circadian variations of VM attacks. However, what is the possible mechanism in the occurrence and clinical presentation of VM underlying the circadian rhythm? The pathophysiology of VM has not been fully established yet(19, 20). In present hypotheses, as a a variant of migraine, VM is the integral overlap among vestibular pathways, migraine circuit triggers and central mechanisms for premonitory symptom generation(21-23).Hypothalamic activation and circadian variation has been reported during migraine attacks in many recently studies(16, 24, 25). The circadian rhythm is controlled by a complex system of molecular regulation with a master precursor, located in the suprachiasmatic nucleus of the anterior hypothalamus(26, 27). In pathophysiological model of VM by Furman, the hypothalamus was contained within a network of interoceptive circuits for vestibular, visceral sensory, and nociceptive information(28).Therefore, the circadian variations in the occurrence and the clinical presentation of VM may due to the hypothalamic involvement in both nociception and circadian periodicity(28).

Similar to the migraine, peak incidence of VM is usually during sleep or upon awakening(9, 29). A key question is whether the observed temporal pattern represents a true endogenously mediated circadian pattern, or it is just triggered by alteration of the sleep pattern. However, the proportion of attacks induced

by abnormal sleep did not increase significantly in VM patients with morning onset. Lack of sleep may indeed be one of the triggers of attacks, but endogenously circadian rhythm of VM maybe dominant.

Our data should be interpreted with some caution due to limitations of the study. These included the relatively small sample size and retrospective bias inherent. Secondly, we enrolled patients with probable VM, who might develop definite VM over time as some studies have shown(30-32). Moreover, we only described the clinical features of VM by a cross-sectional study, further study on the relevant mechanism will be great helpful to identify this entity.

Conclusion

In summary, occurrence and clinical presentations of vestibular symptoms exhibited circadian variations. Our finding may suggest chronobiological mechanisms in VM and aid in improving clinical treatment options.

Abbreviations

VM: vestibular migraine; ICHD-3: the third version of the International Classification of Headache Disorder; ANOVA: analysis of variance.

Declarations

Ethics approval and consent to participate

This study involving human participants were reviewed and approved by the Institutional Review Board (IRB NO, 2019-LYP-030) and all patients gave informed consent.

Consent for publication

Not applicable.

Availability of data and materials

Original data of the present study are available from the corresponding author upon reasonable request.

Competing interests

All the authors declare no conflict of interest.

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Authors' contributions

WL, LY, YY, and WD designed the study. WL, HD, HQ, HZ, YY and WD evaluated the subjects and collected the data. LY and YY analyzed the data. WL wrote the initial draft, with YY and WD participating in revising the manuscript.

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Tables

Table 1 The characteristics of patients with VM.

Variable	Patients (n =189)
Age in years, median (IQR)	42 (35.00, 52.00)
Gender (female), n (%)	189 (100.00)
Race, n (%)	189 (100.0)
Age of onset, median (IQR)	36.00 (29.50, 44.00)
Duration of illness, years, median (IQR)	4.00 (1.00, 8.00)
History of alcohol, n (%)	2 (1.10)
History of caffeine, n (%)	21 (11.10)
History of motion sickness, n (%)	120 (63.50)
Family history, n (%)	71 (37.60)

Table 2 Circadian variation in clinical presentation of 189 female VM patients.

	Total (N=189) N(%)	00:00 –05:59 (N=68) N(%)	06:00 –11:59 (N=72) N(%)	12:00 –17:59 (N=28) N(%)	18:00 –23:59 (N=21) N(%)	P value	Post-hoc analysesd
All attacks	189 (100.0)	68 (100.0)	72 (100.0)	28 (100.0)	21 (100.0)	-	-
Activities at onset							
Moving	46 (24.3)	3 (4.4)	11 (15.3)	16 (57.1)	16 (76.2)	<0.001	3=4>2=1
Rising	69 (36.5)	22 (32.4)	45 (62.5)	2 (7.1)	0 (0.0)	<0.001	2>1>3>4
Sitting	19 (10.1)	2 (2.9)	7 (9.7)	5 (17.9)	5 (23.8)	<0.001	4>3=2>1
Sleeping	55 (29.1)	41 (60.3)	9 (12.5)	5 (17.9)	0 (0.0)	<0.001	1>2=3=4
Vestibular symptoms							
Spontaneous vertigo	80 (42.3)	34 (50.0)	22 (30.6)	11 (39.3)	13 (61.9)	0.028	1=2=3=4
Orthostatic vertigo	43 (22.8)	14 (20.6)	24 (33.3)	2 (7.1)	3 (14.3)	0.025	2>1=4>3
Head motion induced vertigo	41 (21.7)	19 (27.9)	14 (19.4)	5 (17.9)	3 (14.3)	0.500	-
Visually induced vertigo	9 (4.8)	1 (1.5)	1 (1.4)	5 (17.9)	2 (9.5)	0.003	3>4>1=2
Dizziness	55 (29.1)	15 (22.1)	19 (26.4)	16 (57.1)	5 (23.8)	0.005	3>4>1=2
Accompanying symptoms							
Headache	66 (34.9)	19 (27.9)	29 (40.3)	12 (42.9)	6 (28.6)	0.319	-
Bilateral neck pain	42 (22.2)	20 (29.4)	15 (20.8)	6 (21.4)	1 (4.8)	0.103	-
Photophobia	111 (58.7)	39 (57.4)	45 (62.5)	18 (64.3)	9 (42.9)	0.389	-
Visual aura	9 (4.8)	2 (2.9)	3 (4.2)	2 (7.1)	2 (9.5)	0.465	-
Visual blurring	31 (16.4)	10 (14.7)	12 (16.7)	6 (21.4)	3 (14.3)	0.867	-

Phonophobia	104 (55.0)	38 (55.9)	43 (59.7)	15 (53.6)	8 (38.1)	0.374	-
Tinnitus	25 (13.2)	9 (13.2)	7 (9.7)	4 (14.3)	5 (23.8)	0.387	-
Nausea and vomiting	113 (59.8)	39 (57.4)	44 (61.1)	18 (64.3)	12 (57.1)	0.915	-

Figures

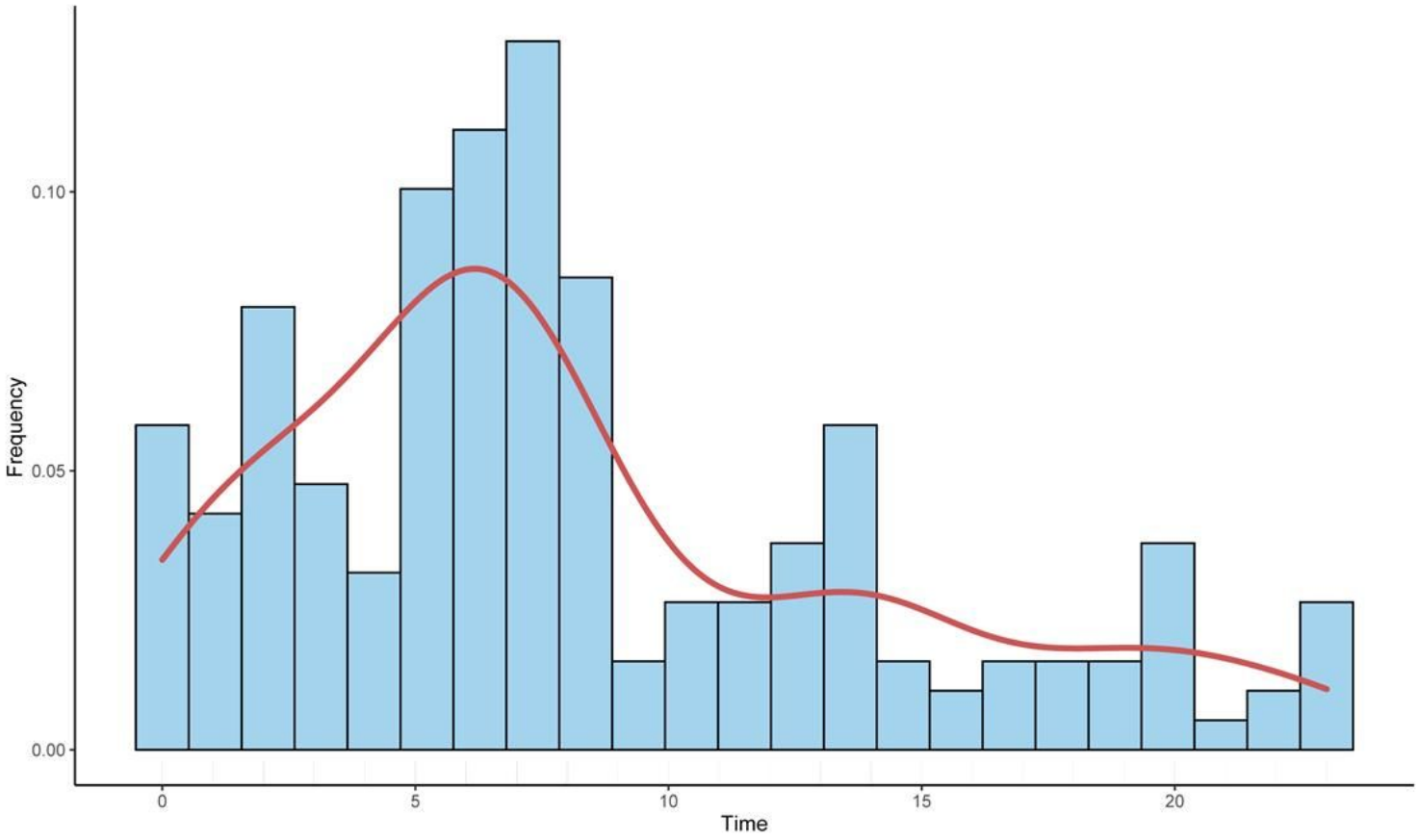


Figure 1

Kernel density for the circadian variation in VM occurrence. The peak of occurrence was at about 7 o'clock in the morning.

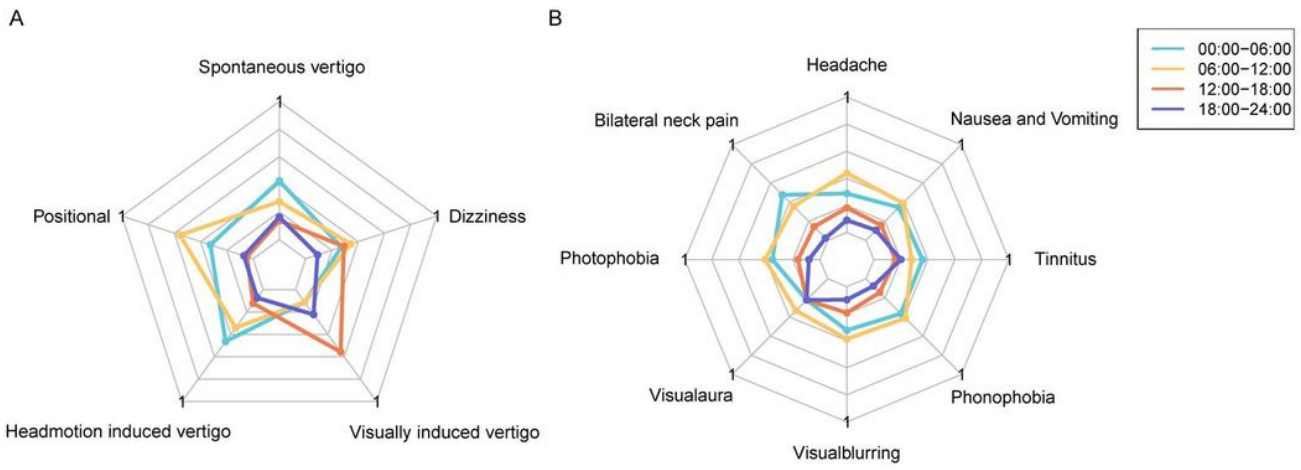


Figure 2

The radar plots for the circadian variation in clinical presentation of VM by comparing them among four 6-hour quadrants per day: 00:00-05:59, 06:00-11:59, 12:00-17:59, 18:00-23:59. A: vestibular symptom during attacks of VM; B: accompanying symptoms during attacks of VM.

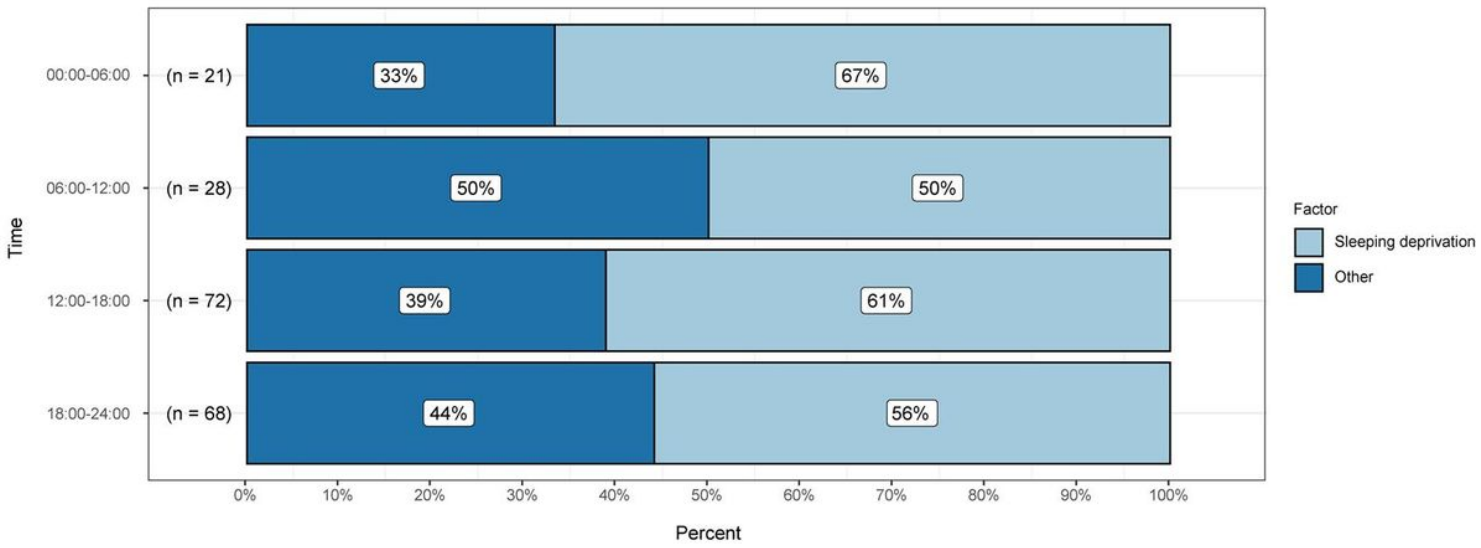


Figure 3

The 100% stacked bar for the self-reported triggers of VM attacks by comparing them among four 6-hour quadrants per day. The percentage of sleep deprivation showed no significant difference among four quadrants. (P>0.05)

Supplementary Files

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