〈Regular Article〉

Accuracy of short-term insomnia onset and composite clinical score in the differential diagnosis of common cold and influenza: A cross-sectional study

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ABSTRACT Influenza (IA) and the common cold (CC) may present with similar symptoms. However, rapid IA diagnostic tests have a low sensitivity during the early stages of the disease. Therefore, various diagnostic tools are needed. Mild short-term insomnia (MSTI) occurs in patients with CC, but the incidence in patients with IA remains unknown. Hence, we hypothesized the difference between the day of onset of MSTI and the date of fever occurrence in IA to be shorter than that in CC. This study aimed to investigate the incidence of MSTI in patients with CC and IA with fever (≥ 37.5℃) and the risk of developing acute-onset MSTI (alone or as part of a composite clinical score) to aid in the differential diagnosis during the early disease stage. The relationship between MSTI and other symptoms was analyzed using quadratic logistic regression to model the number of IA cases with composite score day progression from the onset of fever, namely origin day 0. The results revealed a day 0 axis-symmetrical and inverted U-shaped relationship between the onset days of the composite scores and estimated probability of IA. The coefficient of the quadratic term is negative and significantly different from zero, supporting the hypothesis that the onset of IA-related MSTIs is more acute than that of CC-related MSTIs. Principal component analysis was also applied to the onset days for five IA- and CC-related symptoms, in addition to fever (MSTI, cough, rhinorrhea, sore throat, and headache). The maximum day difference in fever onset and at least one additional symptom was established as the cutoff day between IA and CC using receiver operating characteristic analysis. The cutoff value was confirmed based on the MSTI-onset-derived variables using logistic regression. This cross-sectional survey included 100 and 106 CC and IA patients, respectively. The optimal cutoff day were one day before and one day after the onset of fever. For those with CC and MSTI beyond the cutoff day, the diagnostic sensitivity, specificity, and positive likelihood ratio were 7%, 99%, and 7.42, respectively. For patients with CC and any composite clinical score symptoms beyond the cutoff day, the sensitivity, specificity, and positive likelihood ratios were 36%, 92%, and 4.77, respectively. A composite clinical score and MSTI onset with a cutoff day of one day before and after fever

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onset may help distinguish between early stage CC and IA.

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INTRODUCTION

Respiratory infections, including influenza (IA) and common cold (CC), may present with similar symptoms. Antiviral drugs have minimal therapeutic benefits if initiated more than 48 hours after IA onset[1]. The rapid influenza diagnostic test (RIDT) has 35% sensitivity and 100% specificity within 12 h and 66% sensitivity and 97% specificity between 12 h and 24 h[2]. During an IA epidemic, excluding IA during disease onset is difficult even if the RIDT result is negative. Therefore, additional diagnostic tools should be developed to differentiate between IA and CC.

IA has a more acute onset compared with CC[3]. However, CC often presents with acute onset. Currently, there is no established model to distinguish acute-onset CC from IA. Several studies have proposed various tests to distinguish IA from IA-like illnesses[4]. However, diagnosing IA remains a challenge[5]. Patients with CC and IA also exhibit overlapping symptoms. Cough and headache are more common in IA than in CC[6]. Sore throat and rhinorrhea are common CC symptoms (ICD10, J100)[7]. Therefore, the precise quantification of the onset of CC or cold-like illnesses should be established.

Mild short-term insomnia (MSTI) frequently begins during early CC stages[8]. Gomi first described the MSTI in 2019[8]. It occurs in 75% (24 / 32) of patients with CC a few days before and after CC onset and lasts up to several days. The use of the MSTI as a potential criterion to distinguish between CC and IA has not yet been established. However, determining the association of MSTI with IA and CC may aid in differential diagnosis during the early stages of the two conditions, reducing unnecessary examinations, re-examinations, and anti-IA drug prescriptions. Moreover, a composite measure would assist healthcare providers and patients in differentiating CCs from IAs. Similar techniques may also aid in the differential diagnosis of other diseases including coronavirus disease 2019.

If IA presents with a more acute MSTI onset than CC, MSTI may have diagnostic value in distinguishing IA from CC. The hypothesis is that the difference between the day of onset of MSTI and the date of fever occurrence in IA is smaller than that in CC.

This study aimed to propose a new statistical model to aid in the differential diagnosis of CC and IA with fever (≥ 37.5℃) by evaluating the occurrence of acute-onset MSTI in patients.

MATERIALS AND METHODS

Study design and ethical approval

This cross-sectional study was conducted at an outpatient family medicine clinic in Nagano, Japan, between December 1, 2018, and February 28, 2019. Enrollment was limited to patients with a fever. This study was conducted in accordance with the 1964 Declaration of Helsinki guidelines. This study was approved by the ethics committee of the Japan Primary Care Association (approval number: 2019-007). Patients were informed that the data obtained would be used for research purposes. The completion and return of the questionnaires confirmed participants' consent. All data were anonymized and all participants were allowed to refuse to participate at any point without any repercussions.

Enrolled participants

A medical checklist questionnaire was administered to all the patients. The symptoms

were confirmed during a diagnostic interview with a physician. Based on the questionnaire, details regarding the length of illness and nature of the symptoms were obtained. The questionnaire included a checklist of the following symptoms: fever, sore throat, cough, sputum, rhinorrhea, joint pain, headache, abdominal pain, back pain, nausea, vomiting, weight loss, weight gain, diarrhea, constipation, loss of appetite, cold, shivering, difficulty in breathing, fatigue, dizziness, and insomnia. For each question, a checkbox and free-response field were indicated. Following the diagnosis of a respiratory illness, new symptoms were added to the list if they were consistent with the diagnosis. MSTI assessment was performed using the following question: 'Did you sleep as usual?' Only symptoms that were apparent to family members or guardians were described to patients who could not express their symptoms. MSTI length was determined to be a single day. Many patients with respiratory infections could not precisely recall when they woke up or the number of nighttime awakenings due to their illness.

Fever was defined as an axillary temperature of ≥ 37.5℃. The day of fever onset was defined as the day when the patient was first aware of fever. In particular, this also included temperatures within a 37.0-37.5℃ range on that day. Fever onset was defined as the day of disease onset.

Short-term insomnia was defined as difficulty in falling asleep, awakening at night, or waking early in a person who typically sleeps well. All patients diagnosed with CC or IA were included in the study and divided into CC and IA groups. IA was diagnosed in a patient with a positive RIDT result and a fever. CC was diagnosed based on the physician's clinical judgment and negative RIDT results and coded as J00 (acute nasopharyngitis) according to the 10th revision of the International Classification of Diseases (ICD-10)[7]. Atypical J100 cases were excluded, including those with cough only, rhinorrhea only, J100 with diarrhea, and other diseases. Patients who did not undergo RIDT or had other illnesses were excluded. Patients whose medical records did not include the day of symptom onset were also excluded. The criteria for selecting

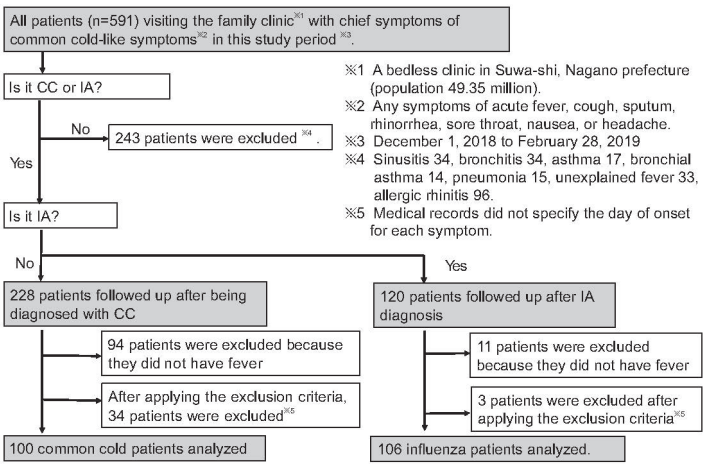

Fig. 1. Study flowchart

The CC group included patients with fever, with two or more symptoms of cough, rhinorrhea, sore throat, and headache; with RIDT negative test; who were assigned an ICD-10 code J00; who were judged as not having a disease other than J00 in the ICD-10, and whose time of appearance of each symptom was not indicated in the chart.

-IA group: patients with fever, with two or more symptoms of cough, rhinorrhea, sore throat, and headache; RIDT-positive results; who were judged as not having a disease other than influenza; whose onset of each symptom was not indicated in the chart

the group of participants are shown in Fig. 1.

The QuickNavi-Flu kit (Denka Seiken, Tokyo, Japan) was used to perform the RIDT. The detection limit of this kit was examined and its performance was comparable to that of other commercial kits[9].

Data on IA/CC, cough, headache, sore throat, MSTI, sex, and age were collected. The minimum sample size was 80, based on a minimum of 10 events per variable rule[10].

Statistical analyses

Principal component analysis was applied to the onset days of five IA- and CC-related symptoms, aside from fever (MSTI, cough, rhinorrhea, sore throat, and headache). The scores of the first principal component (65.7% of the total variance) were used as a composite clinical symptom variable, S1 − representing the distance (number of days) from the origin − and day 0 (fever onset). However, as this was not sufficiently accurate to describe temporal changes in the ratio of IA to CC, a quadratic term S2, defined as the square of S1 was also introduced to increase precision. Similarly, an MSTI onset variable, M1, was defined as the distance (number of days) from day 0, and M2 as the square of M1. To distinguish IA from CC based on differences in the day of onset, the presence of fever and the other five symptoms and the maximum difference in days between fever onset (day 0) and the onset of at least one of the five symptoms were calculated. The maximum day difference was determined using receiver operating characteristic (ROC) analysis with the Youden's index. It was used as a cutoff point to distinguish between IA and CC. Probabilistic measures, including specificity, sensitivity, positive likelihood ratios (LH+), negative likelihood ratios (LH-), and their 95% confidence intervals (CIs)[11], were used to assess the relationship between CC and IA. The ROC curve cutoff value within 24 h was determined as a single day. The relationship between MSTIs and other symptoms was analyzed using logistic regression. Quadratic logistic regression was used to model the number of IA cases with composite score day progression from fever onset. The variance inflation factor (VIF) was used to detect multicollinearity between variables. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using R 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria)[12]. Odds ratios (ORs) were calculated using Fisher's exact test for the univariate analysis and multiple logistic regression for the multivariate analysis.

MSTI, cough, rhinorrhea, sore throat, and headache are collectively referred to as 5Sx. The presence of symptoms was considered positive for 5Sx, whereas the absence of all symptoms was considered negative for 5Sx. Any 5Sx symptoms that developed on a day other than day 1 were referred to as 5Sx-OD1, which was considered positive if the patient developed 5Sx outside the range of -1 to 1 d.

Any symptom that developed on any day other than day 1 was marked with the suffix "OD1." These variables were referred to as MSTI-OD1, cough-OD1, rhinorrhea-OD1, sore throat-OD1, and headache-OD1. Any symptom that developed on any day other than day 0 was marked with the suffix "OD0."

RESULTS

All patients (n = 591) with CC-like symptoms, including acute fever, cough, sputum production, rhinorrhea, sore throat, nausea, and headache, were included in the analysis. In total, 243 patients were excluded because they were not diagnosed with CC or IA. Five patients were excluded because their medical records did not indicate the day of the symptom onset. Furthermore, 105 patients with fever were excluded because their temperatures did not meet the inclusion criteria. During the IA season, from December to February, 100 patients

with CC (51 men; age range: 0.67 - 80 years) and 106 patients with IA (57 men; age range, 1- 8 1 years) were enrolled (Table 1).

Akaike's information criterion (AIC) was used to compare the fitness of the quadratic model, including the variable S2 or M2, with that of the linear model, excluding them in the logistic regression for the temporal trend of IA / CC, adjusted for age and sex. Consequently, the quadratic model best fit the collected data (composite clinical score: linear AIC = 284.70, quadratic AIC = 279.96; MSTI: linear AIC = 163.82, quadratic AIC = 156.85). All variables had a VIF value of less than two; therefore, no multicollinearity problem was observed between the variables.

The logistic regression of composite scores showed that the quadratic term S2 alone was significantly negative (Table 2), suggesting a symmetrical day 0 axis and an inverted U-shaped relationship between the onset days of composite scores and the estimated probability of IA (Fig. 2a). Similarly, the logistic regression of the MSTI showed that the quadratic term M2 alone was significantly negative (Table 3), suggesting a day 0 axis-symmetrical and an inverted U-shaped relationship between the onset days of the MSTI and the estimated probability of IA (Fig. 2b). Therefore, as the day progressed, both composite scores and

Table 1. Characteristics and comparisons between patients with common cold and those with influenza

	Common cold (n = 100)	Influenza (n = 106)
Male, n (%)	51 (51)	57 (54)
Female, n (%)	49 (49)	49 (46)
Age (years), mean (SD)	27.9 (21.4)	28 (22)
Age group (years), n (%)		
≤ 9	30 (30)	28 (26)
10 - 19	24 (24)	32 (30)
20 - 49	30 (30)	26 (25)
≥ 50	16 (16)	20 (19)

SD: standard deviation

Table 2. Results from multiple logistic regression analysis showing the relationship between the onset days of the composite clinical symptom score and the estimated probability of IA

	Adjusted odds ratios with 95% confidence intervals	p value
S1	0.96 (0.78 - 1.2)	0.742
S2	0.95 (0.9 - 0.99)	0.022*

The odds ratios were adjusted for age and sex. Statistical significance was set at $p < 0.05$.
IA, influenza; S1, onset days of the composite clinical symptom score; S2, square of S1

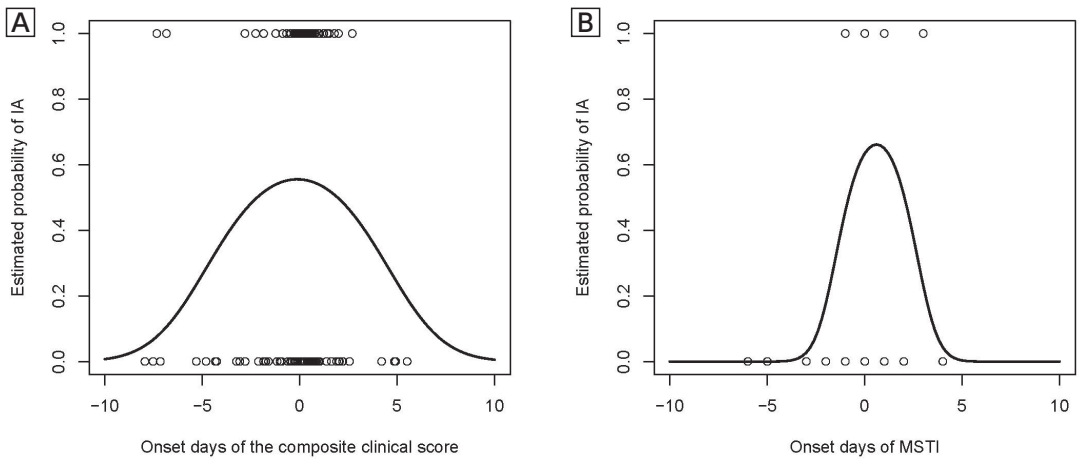

Fig. 2. Quadratic logistic regression estimates the likely proportion of patients with confirmed IA in a sample comprising patients with CC and IA. The horizontal axis represents the composite onset days of five symptoms (insomnia, cough, rhinorrhea, headache, and sore throat) derived from the principal component analysis (A) and the onset day of insomnia (B). The curve represents the quadratic logistic regression with a single significant variable and the number of days squared. CC, common cold; IA, influenza

MSTI increased in IA cases, peaked on day 0, and decreased thereafter.

The diagnostic cutoff day for which the presentation of symptoms indicated and increased the likelihood of CC was 1.00 (day 1). Therefore, the diagnostic cutoff day for MSTI was determined to be day 1, as the cutoff value was < 1 d.

Compared to IA, the sensitivity, specificity, LH-positive value, and LH-negative value of 5Sx-OD1 for CC were 36%, 92%, 4.77, and 0.69, respectively. These results were statistically significant (Table 4). The sensitivity, specificity, LH+, and LH- of the MSTI-OD1 for CC were 7%, 99%, 7.42, and 0.94, respectively. This result was statistically significant (Table 4).

Table 3. Results from multiple logistic regression analysis showing the relationship between the onset days of MSTI and the estimated probability of IA

	Adjusted odds ratios with 95% confidence intervals	p value
M1	1.52 (0.88 - 2.64)	0.14
M2	0.7 (0.5 - 0.98)	0.036*

The odds ratios were adjusted for age and sex. Statistical significance was set at $p < 0.05$.
MSTI, mild short-term insomnia; IA, influenza; M1, onset days of MSTI; M2, square of M1

DISCUSSION

In our study, MSTIs were a significant symptom of IA. Moreover, logistic regression analysis identified the MSTI as an independent event associated with rhinorrhea and cough. The probability of IA to CC estimated from quadratic logistic regression showed a day 0 axis-symmetrical and inverted U-shaped temporal variation in both the composite symptom variable (Fig. 2a) and the MSTI onset variable (Fig. 2b). The coefficient of the quadratic term was negative and significantly different from zero for both the variables (Tables 2 and 3). These results support the hypothesis that the onset of IA-related MSTIs is more acute than CC-related MSTIs. In patients with upper respiratory tract inflammation and fever during the IA season, the occurrence of MSTI or 5Sx-OD1 before and after one day of fever is suggestive of CC and not IA. This study proposes a model for quantifying "rapid onset," which distinguishes IA from CC. This hallmark strongly suggests that combined quadratic logistic regression and principal component analyses can help define

Table 4. Univariate analysis results of the characteristics of patients with common cold versus that of patients with influenza

	CC (n = 100)	IA (n = 106)	Sensitivity	Specificity	LH+	LH-	OR	95% CI	p-value	AUC
MSTI	54	63	54%	41%	0.91	1.13	0.80	**0.46 - 1.40**	0.48	
MSTI-0	**24**	**42**	**24%**	**60%**	**0.60**	**1.23**	**0.48**	**0.26 - 0.91**	**0.02**	
5Sx-OD1	36	8	36%	92%	4.77	0.69	6.83	**3.1 - 16.5**	< 0.01*	
MSTI-OD0	30	20	30%	81%	1.59	0.86	1.84	**0.92 - 3.68**	0.07	
MSTI-OD1	7	1	7%	99%	7.42	0.94	7.84	**1.06 - 177**	0.03	0.62
Cough-OD1	16	4	16%	96%	4.24	0.87	4.82	**1.50 - 16.25**	< 0.01*	0.60
Rhinorrhea-OD1	23	5	23%	95%	4.87	0.81	5.98	**2.12 - 17.19**	< 0.01*	0.63
Sore throat-OD1	13	2	13%	98%	6.89	0.89	7.70	**1.67 - 48.95**	< 0.01*	0.67
Headache-OD1	7	0	7%	100%	Inf	0.93	Inf	**1.89 - Inf**	< 0.01*	0.55

CC, common cold; IA, influenza.
Odds ratios and p-values were calculated using Fisher's exact test.
Statistical significance was set at $p < 0.05$.
Inf, infinity
MSTI: mild short-term insomnia
MSTI-0, mild short-term insomnia that occurred on day 0, and fever onset.
5Sx, five symptoms (MSTI, cough, rhinorrhea, sore throat, and headache)
The presence of any of the symptoms was considered positive for 5Sx, while the absence of all symptoms was considered negative for 5Sx.
OD1, suffix for a symptom that developed on a day other than day 1
LH+, positive likelihood ratio
LH −, negative likelihood ratio
AUC, area under curve

clinically useful cutoff points to obtain an accurate diagnosis.

Theoretically, MSTI onset should be considered within hours rather than days. However, this is not realistic, because sleep typically occurs at night. Few people recall waking hours, particularly when they are ill. Moreover, the 24-h unit was not diagnostically functional. Therefore, the most practical approach is to determine the MSTI onset in days. In this study, all cutoff values were determined within one day, indicating that a cutoff on the day of onset (day 0) might not be useful. Several considerations have been considered from a clinical perspective. The model developed in our study required a non-IA diagnosis to confirm the presence of CC and a reduction in false-positive IA cases. Hence, day 0 was not a realistic cutoff. Thus, a range of ± 1 d was considered suitable. High LH+ levels were observed in the 5Sx-OD1 and MSTI-OD1 groups, indicating their diagnostic effectiveness.

Some guidelines suggest cough as a diagnostic determinant[6]. However, coughing was not associated with a high sensitivity or specificity in this study, which may have affected the guidelines for RIDT use. Some patients with IA who tested negative in the RIDT may have been included in the CC group. However, these patients could not be excluded from this study. In a previous study[8], the sensitivity, specificity, LH+, and LH- were 19%, 99%, 19.9, and 0.82, respectively, in the CC group (n = 32) with the MSTI-OD1 (n = 6). The values in the previous study exceeded those in the current study, implying a higher clinical significance of MSTI-OD1 positivity compared with that suggested by our present results. The number of patients with MSTI-OD1 who were diagnosed with IA did not depend on the accuracy of RIDT[9]. However, depending on the RIDT kit type, patients with IA may be misdiagnosed with CC owing to the low test sensitivity. As MSTI-OD1 may appear before the onset of fever, physicians may be able to distinguish between IA and CC in patients with early IA despite a negative RIDT result. However, RIDT is not available in several countries.

The results of this study may reduce unnecessary medication use, tolerance risk, number of medical visits, and prescribed sleep agents by facilitating accurate differential diagnosis between patients with IA and CC. Inappropriately prescribed IA medications may increase the risk of side effects[13] or lead to drug-resistant infections caused by viruses[14]. Therefore, doctors must be able to precisely distinguish between patients who may or may not benefit from anti-IA medications. MSTI-OD1 may play an important role; however, its low sensitivity (7%) and high specificity (99%) should be considered when using MSTI-OD1 for IA assessment (Table 4).

As RIDT yields many false-negative results, IA cannot be ruled out in patients with CC-like pathology even if the RIDT result is negative. However, if patients with CC-like symptoms had a negative RIDT result and were positive for MSTI-OD1, they were more likely to have CC than IA. Therefore, these criteria may contribute to the accurate diagnosis of IA.

Patients who were taking oral medications were excluded from the study. As many patients with cold-like symptoms take over-the-counter drugs, excluding them is not a suitable diagnostic tool for clinical practice.

This study had several limitations. First, the selection of onset-defining symptoms may have introduced a bias. Second, this study did not consider the inherent differences between the patients who were more likely to have positive and negative RIDT results. Third, as only one researcher conducted this study, the inter-rater reliability of diagnostic categorization is unknown and should be assessed in the future. Fourth, recall and reporting biases might have affected data collection, as the

patients only reported their symptoms in response to a direct question. Fifth, this study only included patients with fever; hence, future studies should expand the participant eligibility. Finally, the methods utilized did not differentiate between CC and IA over a period of less than a day.

In conclusion, during the IA season, MSTI, cough, rhinorrhea, sore throat, and headache appeared on days other than day 1 before or after the onset of fever and were more likely caused by CC than IA. Thus, our results may differ between patients with CC and IA during an IA epidemic.

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DECLARATIONS OF INTEREST

None

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