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Possible Risks and Protective Factors of Upper Respiratory Tract Infections in Healthy Japanese Office Workers

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Abstract

Objective: In order to determine the risks and protective factors of upper respiratory tract infections (URTIs) in healthy office workers, we conducted a preliminary epidemiological survey and analysis of saliva parameter levels.

Methods: One hundred and forty-six (98 men, 48 women; aged 20-59 years) healthy, full-time office workers in Tokyo and its suburbs participated in a questionnaire survey on lifestyle habits and daily physical condition, including symptoms of URTIs, from October 2012 to March 2013. Salivary parameters (secretory IgA, beta-defensin 2, LL-37, granulysin, lysozyme, cortisol) levels were also measured to analyze the correlation to URTI incidence and lifestyle habits.

Results: Both the incidence rate and frequency of URTIs per person during the investigation period were highest among participants in their 50s and lowest among participants in their 30s. Participants who lived with their family showed higher URTI incidence than those who lived alone, while those with exercise habits showed lower URTI incidence. Higher saliva cortisol levels significantly correlated with high URTI incidence, while higher salivary granulysin levels significantly correlated with low URTI incidence.

Conclusions: The risk factors of URTI incidence among healthy, full-time office workers include not only aging, but also living with family and higher salivary cortisol levels, and the protective factors are exercise habits and higher salivary granulysin levels.

Keywords: Common cold; Cortisol; Exercise; Granulysin; Upper respiratory tract infections

Abbreviations

URTI: Upper Respiratory Tract Infection; BD2: Beta-Defensin 2; sIgA: Secretory Immune Globulin A

Introduction

Upper respiratory tract infections (URTIs), including the common cold and influenza, are disorders caused by the infection of upper respiratory tract mucosa with pathogens (mainly viruses such as Rhinovirus), and are accompanied by symptoms such as fever, sore throat and cough [1]. Although URTIs are a "common" disorder among healthy people in daily life, there is no specific medication and they often require a few days of complete rest for recovery. Some full-time office workers in metropolitan cities such as Tokyo are faced with a high risk of URTIs since they spend a lot of time in crowds and have many opportunities to catch viruses from infected people. Many also experience fatigue and mental stress caused by complicated business relationships, which might weaken the immune defense system [2]. Furthermore, it is difficult for office workers to change their schedules to take sudden absences due to illness. For these reasons, the prevention of URTIs is an important subject.

Although some reports have provided evidence that gargling habits [3] and the intake of probiotics [4] are effective in preventing URTIs among healthy adult volunteers, there are few reports indicating other lifestyle habits that could be effective for office workers [5,6]. Therefore, we conducted a preliminary epidemiological survey to determine the risks and protective factors of URTIs in the daily lives of healthy office workers. Our survey includes a questionnaire about 10 lifestyle habits that are known as possible risks and protective factors against URTIs, and daily questionnaires about physical condition including symptoms of URTIs. A physician evaluated these in interviews with participants every 10 weeks.

Salivary immune defense factors are featured as protective factors against URTIs. For example, salivary sIgA is considered one of the most important first-line defense factors against pathogen invasion in the mucous membrane tissue. Dimer IgA secreted by plasma cells in the saliva glands is transported through the salivary epithelial cells by bounded polymeric Ig receptors and is then released into the saliva with a secretory component. This secreted sIgA bonds to pathogens to protect against infection [7]. Therefore, we analyzed several saliva parameter levels including sIgA to determine the correlation with URTIs in the present study.

Materials and Methods

Ethical approval and consent to participate

This study was conducted in accordance with the latest amendment of the Helsinki Declaration and the Guidelines for Epidemiological Research established by the Japanese Ministry of Health, Labour and Welfare. All procedures were approved by the Institutional Review Board of the Chiyoda Paramedical Care Clinic. Written, informed consent was obtained from all participants after they had been warned of the possible risks and disadvantages.

Participants

In total, 169 healthy, full-time office workers (aged 20-59 years) in Tokyo and its suburbs were recruited via Internet advertising. The 153 participants who satisfied the selection criteria started our preliminary epidemiological survey trial, and 146 (the breakdown is indicated in Table 1) completed it. The exclusion criteria were as follows: (1) persons from whom it was difficult to collect saliva; (2) persons with pollinosis, chronic rhinitis, or asthma; (3) persons with periodontitis or gingivitis; (4) persons with a history of serious liver, kidney, heart, lung or gut diseases; (5) persons taking drugs or supplements that might affect the outcome of this study; (6) persons with pregnancy (including possible pregnancy) and breast-feeding; and (7) persons deemed ineligible for this study by a physician.

	Age groups				
	20s (n)	**30s (n)**	**40s (n)**	**50s (n)**	**Total**
Male	22	22	27	27	98
Female	10	12	13	13	48
Total	32	34	40	40	146

Table 1: Participants.

Survey

A survey on the incidence rate of URTIs was performed from October 2012 to March 2013 at the Chiyoda Paramedical Care Clinic (Tokyo, Japan).

Before the survey, participants filled out a questionnaire on the following lifestyle habits: (1) Diet: intake of a well-balanced meal three times (breakfast, lunch, dinner) everyday/unbalanced meal intake; (2) Sleep: adequate sleep (more than 6 hours)/lack of sleep (less than 6 hours); (3) Alcohol consumption: a little (less than 3 times per week)/ frequent (more than 3 times per week) (4) Smoking: no (never or past)/yes (present); (5) Exercise: no (or yes but for less than 1 year)/yes (for more than 1 year; (6) Bowel movements: regular (almost daily)/ irregular (tend to be constipated or have frequent diarrhea); (7) Gargling: no (rarely)/yes (always or sometimes); (8) Hand washing: no/yes; (9) Supplementation with probiotics: no/yes; and (10) Living with family: no/yes.

During the URTI survey period participants kept diaries about their physical condition including symptoms of URTIs such as: (1) fever, (2) chills, (3) headache, (4) runny nose, (5) stuffy nose, (6) sneezing, (7) cough, (8) sore throat, (9) sputum, (10) malaise, (11) muscular pain, (12) joint pain, (13) nausea, (14) diarrhoea, (15) stomachache and (16) body temperature. The occurrence of URTIs was evaluated by a physician based on the information in the health diaries and interviews with participants every 10 weeks.

Saliva analysis

Saliva was collected at the clinic in the morning hours of the day before the survey by the passive drool method. That is, participants were asked to pool saliva in the mouth for 3 min, then to transfer it to a collection tube via a straw. This saliva collection was repeated four times with intervals of 1 min. The saliva sample was centrifuged at 1500 *g* for 15 min, and the supernatant was stored below -20°C until analysis. The levels of secretory immune globulin (sIgA; Salivary sIgA Indirect Enzyme Immunoassay Kit, Salimetrics, PA, USA), beta-defensin 2 (BD2; Human Beta-defensin 2 ELISA Kit, Phoenix, CA, USA), granulysin (Anti-granulysin RB1, Biotin Labeled Anti-granulysin RC8, MBL, Nagoya, Japan), lysozyme (Human Lysozyme ELISA Kit, Assay Max, Assaypro, MO, USA), cortisol (Expanded Range, High Sensitivity, Salivary Cortisol Enzyme Immunoassay Kit, Salimetrics), and LL-37 (Human LL-37 ELISA Kit, Hycult Biotech, Uden, Netherlands) were determined according to the relevant instruction manuals.

Statistical analyses

All analyses were performed using SPSS 20.0 (IBM Japan, Tokyo, Japan) for the chi-square test (for incidence of URTI among some groups), the Games-Howell test (for number of occurrences of URTIs by age groups), the Tukey-Kramer test (for days of URTI duration or saliva parameter levels by age groups) and the unpaired t-test (for correlation between lifestyle habits and saliva parameters). Two-tailed p values of <0.05 were considered statistically significant.

Results

URTI incidence rate during survey period

		Infected	**Not infected**	**Incidence**	
Period	**Month**	**(n)**	**(n)**	**%**	**P value[a]**
Weeks 1-4	**October**	18	128	12.3	0.0469
Weeks 5-8	**November**	11	135	7.5	
Weeks 9-12	**December**	25	121	17.1	
Weeks 13-16	**January**	9	137	6.2	
Weeks 17-20	**February**	10	136	6.8	
Weeks 21-24	**March**	8	138	5.5	
Total survey period		64	82	43.8	
Age group	**20s**	15	17	46.9	0.0325
	30s	9	25	26.5	
	40s	16	24	40.0	
	50s	24	16	60.0	

URTI: Upper Respiratory Tract Infection; [a]Chi-square test

Table 2: URTI incidence every 4 weeks and by age group.

The URTI incidence rate for the entire 12 week survey period from October to March was 43.8%. A comparative analysis of the incidence rate every 4 weeks was significantly different (p=0.0469); weeks 9-12 (December) showed the highest incidence rate (17.1%), followed (12.3%) by weeks 1-4 (October), while weeks 21-24 (March) showed the lowest incidence rate (5.5%) (Table 2).

URTI incidence rate between age groups

The incidence rate of URTIs was significantly different between age groups (p=0.0325). It was highest for participants in their 50s (60.0%), second highest for those in their 20s (46.9%), third highest for those in their 40s (40.0%), and lowest for those in their 30s (26.5%).

The cumulative number of URTIs during the survey period was also different between age groups; the average number was smaller for participants in their 20s (0.5 ± 0.6 times) and 30s (0.4 ± 0.8 times), and higher for participants in their 40s (0.8 ± 1.4 times) and 50s (1.2 ± 1.5 times). Notably, participants in their 20s and 30s showed infrequent URTI episodes (up to two times) while participants in their 40s and 50s showed more frequent URTI episodes (up to six times) during the survey period. Statistical analysis of the number of URTI episodes by age group revealed that there was a significant difference between participants in their 30s and 50s (p=0.0486), and a slight difference between participants in their 20s and 50s (p=0.0591). The duration of symptoms per URTI episode did not significantly differ among the age groups (Tables 2 and 3).

		Number of URTI occurrences								Symptom duration
		0 time	1 time	2 times	3 times	4 times	5 times	6 times	Times/person	(days)
		(n)	(n)	(n)	(n)	(n)	(n)	(n)	Mean (SD)	Mean (SD)
Age group	20s	17	14	1	0	0	0	0	0.5 (0.6)	3.2 (1.7)
	30s	25	3	6	0	0	0	0	0.4 (0.8)#	2.9 (1.6)
	40s	24	10	4	0	0	0	2	0.8 (1.4)	3.8 (2.6)
	50s	16	13	7	1	0	2	1	1.2 (1.5)	3.2 (2.0)

URTI: Upper Respiratory Tract Infection; SD: Standard Deviation; #p=0.049 for 30s *vs.* 50s, analyzed with the Games-Howell test

Table 3: Number of URTI occurrences and duration of symptoms per episode by age group.

URTI incidence and lifestyle habits

Lifestyle habit	Status	Infected[a]	Not infected[a]	Incidence	P value[a]
		(n)	(n)	(%)	
Diet	Unbalanced	8	7	53.3	0.4338
	Balanced	56	75	42.7	
Sleep	Lack	6	7	46.2	0.8599
	Adequate	58	75	43.6	
Alcohol consumption	Little/A little	43	63	40.6	0.1949
	Frequent	21	19	52.5	
Smoking	Never/past	48	61	44.0	0.933
	Yes	16	21	43.2	
Exercise	No	56	59	48.7	0.0226
	Yes	8	23	25.8	
Bowel movements	Irregular	9	8	52.9	0.4208
	Regular	55	74	42.6	
Gargling	No	18	15	54.5	0.1587
	Yes	46	67	40.7	
Hand washing	No	17	24	41.5	0.7181
	Yes	47	58	44.8	

Probiotics supplementation	No	53	69	43.4	0.1496
	Yes	11	13	45.8	
Living with family	No	10	27	27.0	0.0171
	Yes	54	55	49.5	

URTI: Upper Respiratory Tract Infection; [a]Chi-square test

Table 4: URTI incidence by lifestyle habit.

The URTI incidence among the participants was analyzed based on their responses to each of the questionnaire items on lifestyle habits in order to derive the risks and protective factors of URTIs. Participants with exercise habits showed a significantly lower incidence rate of URTIs than those without exercise habits (p=0.0226). Furthermore, participants who lived with their family showed a significantly higher incidence rate of URTIs than those who lived alone (p=0.0171). In addition, an unbalanced diet, frequent alcohol consumption, irregular bowel movements, and lack of a frequent gargling habit raised the incidence rate of URTIs by more than 10%, although there was no significant difference (Table 4).

URTI incidence and saliva parameters

We measured initial levels of salivary sIgA, BD2, LL-37, granulysin, lysozyme and cortisol on the day before the survey began. We then calculated the median value of each parameter for 143 participants as three participants were excluded from the analysis because they were infected with URTIs on the measurement day. The URTI incidence rate was significantly lower among participants who had higher saliva granulysin levels than the median value (p=0.0149). The incidence rate was significantly higher among participants who had higher saliva cortisol levels than the median value (p=0.0171) (Table 5).

Saliva parameters	Median value	Relation to median	URTI			
			Infected (n)	Not infected (n)	Incidence (%)	P value[a]
sIgA	260.24 (μg/mL)	Lower	26	45	36.6	0.1065
		Higher	36	36	50.0	
BD2	1237.55 (pg/mL)	Lower	34	37	47.9	0.2776
		Higher	28	44	38.9	
LL-37	18.74 (ng/mL)	Lower	28	43	39.4	0.3476
		Higher	34	38	47.2	
Granulysin	0.937 (ng/mL)	Lower	38	33	53.5	0.0149
		Higher	24	48	33.3	
Lysozyme	29.40 (μg/mL)	Lower	30	41	42.3	0.7915
		Higher	32	40	44.4	
Cortisol	0.279 (μg/dL)	Lower	22	45	32.8	0.0171
		Higher	40	36	52.6	

URTI: Upper Respiratory Tract Infection; sIgA: Secretory IgA; BD2: Beta-Defensin 2; [a]Chi-square test

Table 5: Correlations between URTI incidence and saliva parameter levels.

Relationships between risk factors and protective factors

When the relationships between exercise habits (protective factor of URTIs) and age groups were compared, some significant differences (p=0.0028) were observed: the rate of those with an exercise habit was highest among participants in their 30s (44.1%), second highest among participants in their 20s (31.3%), third highest among participants in their 40s (20.5%), and lowest among participants in their 50s (19.5%).

When the relationships between living with family (risk factor of URTIs) and age groups were compared (p=0.0173), the rate of those living with their family was highest among participants in their 50s (90.2%), second highest among participants in their 40s (80.0%), third highest among participants in their 30s (70.6%) and lowest among participants in their 20s (53.1%).

The rate of those with an exercise habit was nearly equal (p=0.6484) between participants living alone (29.7%) and participants living with their family (26.3%) (Table 6).

When the relationships between salivary granulysin levels (protective factor of URTIs) and age groups were analyzed, the granulysin levels of participants in their 20s (p=0.0243) and 30s

(p=0.0044) were significantly higher than the levels of participants in their 50s. There were no significant differences between salivary cortisol levels (risk factor of URTIs) and age groups, although participants in their 20s showed a slightly higher level than other age groups. In addition, salivary cortisol levels were significantly lower (p=0.0051) among participants living with their family than among participants living alone. Exercise habits indicated relationships with neither salivary granulysin levels nor cortisol levels (Table 7).

Factors		Exercise		Living with family	
		%	P value[a]	%	P value[a]
Age group	20s	31.3	0.0028	53.1	0.0173
	30s	44.1		70.6	
	40s	20.0		80.0	
	50s	19.5		90.2	
Living with family	No	29.7	0.6484		
	Yes	27.3			
[a]Chi-square test					

Table 6: Relationships among the lifestyle factors.

Factors		Granulysin (ng/mL)		Cortisol (μg/dL)	
		Mean ± SD	P value	Mean ± SD	P value
Age group	20s	1.206 ± 1.412	0.0243[a]	0.308 ± 0.133	N.S.[b]
	30s	1.346 ± 1.537	0.0044[a]	0.271 ± 0.138	
	40s	0.966 ± 1.292	N.S.[b]	0.271 ± 0.132	
	50s	0.353 ± 0.619	-	0.272 ± 0.089	
Exercise	No	0.958 ± 1.347	0.7173[c]	0.28 ± 0.13	0.9690[c]
	Yes	0.863 ± 1.07		0.279 ± 0.096	
Living with family	No	1.162 ± 1.455	0.2203[c]	0.339 ± 0.152	0.0051[c]
	Yes	0.86 ± 1.226		0.259 ± 0.105	
SD: Standard Deviation; N.S.: Not Significant; [a]Turkey Kramer test (*vs.* 50s); [b]No significant differences among any age groups when analyzed with the Turkey Kramer test; [c]Unpaired t-test					

Table 7: Relationships between age, exercise habit, living with family, and saliva parameter levels.

Discussion

Risk factors of URTIs

The present study indicated a total URTI incidence rate of 43.8% among 146 full-time office workers in Tokyo and its suburbs during the 6 month (October to March) survey period. The incidence of URTIs was about two-fold higher in December (17.1%) and October (12.3%) than other months (Table 2). These observations were approximately consistent with the statistical data on medical receipts compiled by the Japanese Health Insurance Federation. This data shows that the incidence of URTIs among 661,000 insured people (aged 0-75 years) markedly increased in October compared to September, maintained a high level until December, and then decreased from January to March [8]. Since October is the turning point from autumn to winter in Japan, wide variations in temperature and humidity often occur day to day, and this might contribute to weakened physical condition. December is one of the busiest months of the year because it is an account settlement period for Japanese office workers. In addition, individual lifestyle habits might be disturbed because of the frequent seasonal events such as year-end parties. We speculate that these are the reasons why the incidence of URTIs among office workers was highest in December.

When the incidences of URTIs were analyzed according to age group, the incidence rate was highest for participants in their 50s (60.0%). Furthermore, the frequency of URTIs per person during the survey period was lowest for participants in their 30s. These participants were infected once or at most twice, while participants in their 40s and 50s were infected up to six times (Table 3). The findings are consistent with the fact that immune defenses against pathogens are weakened with age [9]. Therefore, we hypothesize that aging is one of the risk factors of URTIs because of immune system depression.

However, contrary to this hypothesis, participants in their 20s indicated the second highest incidence of URTIs in the present survey (Table 3). A previous report suggested that poor job satisfaction is associated with the common cold [5]. We speculate that office workers in their 20s with low seniority would be exposed to stress at work due to unfamiliar responsibilities and/or overtime work, as well as the need to be attentive to their superiors. Such physiological and mental stresses could cause immune defenses to weaken [2]. In particular, the stress hormone cortisol has the ability to decrease natural killer (NK) cell activity [10], which plays an important role in the prevention of viral infections [11]. In the present study, participants who had higher salivary cortisol levels showed a high URTI incidence rate (Table 5). Furthermore, participants in their 20s showed higher cortisol levels than other age groups (Table 7). Thus, we concluded that high saliva cortisol levels caused by stress, as well as aging, are a risk factor of URTIs.

Interestingly, the duration of symptoms per URTI episode did not significantly differ among the age groups (Table 3). From this observation, we hypothesize that aging weakens the immune system mechanism of vaccination effects against pathogens rather than the immune system mechanism of pathogen elimination.

In addition, it was indicated that some daily lifestyle habits, such as an unbalanced diet, frequent alcohol consumption and irregular bowel movements, increased the URTI incidence rate by more than 10% (Table 4), although more participants would be required to analyze for statistically significant differences. These unfavorable habits also are likely to weaken the immune defense system [2,12].

Participants who lived with their family showed a significantly higher incidence rate of URTIs than those who lived alone (Table 4), suggesting that close contact with family members in the home environment is a more severe risk than contact with many unspecified people at work.

Analyses of the relationships between age groups and living with family showed that participants in their 50s had the highest rate of living with their family (Table 4). This situation, coupled with dysfunction of the immune defense system from aging, might result in a higher risk of URTI. Furthermore, living with family reduces salivary

cortisol levels (Table 7); however, this does not overcome the high risk of close contact with family members in the home environment.

Thus, the present study suggests that the significantly important risk factors of URTIs for full-time office workers include not only aging, but also living with family and higher saliva cortisol levels.

Protective factors of URTIs

Among the habits investigated in the present study, only exercise habits significantly decreased the incidence rate of URTIs (Table 4). Consistent with this result, the analyses of relationships between age groups and exercise suggested that participants in their 30s, the age group with the lowest URTI incidence rate, had the highest rate of exercise. On the other hand, participants in their 50s, the age group with the highest URTI incidence rate, had the lowest rate of exercise (Table 6). There are some reports suggesting that appropriate exercise could enhance immune cell functions, while intensive exercise could suppress immune cell function [13]. In particular, NK cell activity could be enhanced by moderate exercise, as shown by improved survivorship in cancer patients [14].

The present survey did not suggest that gargling has significant protective effects against URTIs (Table 4), although a previous report did indicate that water gargling is effective in preventing URTIs among healthy volunteers aged 18 to 65 years [3]. That report indicated that simple water gargling was more effective than providone-iodine gargling. In our survey, we did not distinguish methods of gargling and this might be the reason that our survey did not indicate the protective effect of gargling.

The present survey did not find significant protective effects of probiotic supplementation on the incidence of URTIs (Table 4), despite some reports having demonstrated that the intake of probiotics showed efficacy against the incidence [15] or duration [16] of URTIs. It is possible that not all probiotics are effective, but specific scientifically-proven probiotics could be effective in reducing the incidence and duration of URTIs [17].

In the present study, five salivary immune defense factors, sIgA [7], BD2 [18], LL-37 [19], lysozyme [19] and granulysin [20] were investigated to analyze the correlation to URTIs. Among these factors, only granulysin reduced the risk of URTI incidence (Table 5).

Granulysin is synthesized in NK cells and cytotoxic T lymphocytes (CTL) as a precursor form. Then, it is cleaved into an active form that has cytolytic activity. The active form of granulysin is released into the intercellular space between target and effector cells, while the precursor form of granulysin is constantly released into the serum [20]. Serum granulysin levels show a positive correlation with the NK cell and CTL cytotoxic activity of peripheral blood. Therefore, serum granulysin levels are used as biomarkers of NK cell and CTL cytotoxic activity in clinical experiments [21]. Furthermore, one report has suggested that granulysin has antibacterial activity and chemoattractant activity [20].

Since we could not find any reports showing a relationship between URTIs and salivary granulysin, we hypothesized three mechanisms in the prevention of URTIs: (1) salivary granulysin levels might be a biomarker of the cytotoxic activity of NK cells and/or CTL resident in the upper respiratory tract mucosa, meaning that participants who had higher salivary granulysin levels would have higher NK cell and/or CTL cytotoxic activity that eliminated virus-infected epithelium cells; (2) salivary granulysin itself might have high antibacterial and/or antivirus activity; and (3) salivary granulysin might activate the immune cells of upper respiratory tract mucosa such as dendritic cells and T lymphocytes, via chemoattractant activity. In the analyses of relationships between age groups and salivary granulysin levels, participants in their 20s and 30s showed higher granulysin levels than participants in their 50s (Table 7). Aging might cause a decrease in salivary granulysin levels. Further studies are needed to reveal the physical importance of salivary granulysin.

It was reported that the decreased saliva sIgA levels among elite professional athletes results in an increased URTI risk [22]. However, the present study did not suggest the protective effect of high sIgA levels for URTIs (Table 5). We presume that the mechanisms of URTI pathogenesis in athletes (participants of previous reports) and office workers (participants of the present study) might be different. For example, athletes who breathe deeply might be affected by bacterial infections in the lungs whereas office workers, who breathe more shallowly, may be affected by virus infections in the upper respiratory tract.

Thus, the present survey suggests that the significantly important protective factors of URTIs for full-time office workers are exercise habits and high saliva granulysin levels.

Conclusions

The results of the present survey suggest that the high risk factors of URTIs for full-time office workers include not only aging, but also living with family and higher saliva cortisol levels, and that regular exercise is a protective factor. Furthermore, it is suggested that higher saliva granulysin levels, which seem to be reduced by aging, is an important immune defense parameter for the prevention of URTIs. To the best of our knowledge, this is the first time such a correlation has been reported.

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Conflicts of interest

All of the authors are employed by Yakult Honsha Co. Ltd. and work in Yakult Central Institute. All sources of funding for this study were from the Yakult Honsha Co. Ltd.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the latest amendment of the Helsinki Declaration and the Guidelines for Epidemiological Research established by the Japanese Ministry of Health, Labour and Welfare. All procedures were approved by the Institutional Review Board of the Chiyoda Paramedical Care Clinic (reference number: YK2012C01). Written, informed consent was obtained from all

participants after they had been warned of the possible risks and disadvantages.

Consent for publication

Written, informed consent including consent for publication was obtained from all participants.

Availability of data and material

The datasets of this study are available from both the corresponding author and Chiyoda Paramedical Care Clinic on reasonable request.

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Authors' contributions

RI, TS, and KS were involved in all aspects of the study; RI wrote the manuscript with TS and KS. KM participated in the conception and study design. All the authors read and approved the final manuscript.

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