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# A Longitudinal Study on Radiation Induced Xerostomia in Radiotherapy of Nasopharyngeal Carcinoma Patients

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## Abstract

**Background:** Xerostomia is the most common post-radiotherapy (post-RT) complication in nasopharyngeal carcinoma (NPC) patients. This longitudinal study evaluated the impact of radiotherapy on saliva flow rate of major salivary glands and patients' quality of life due to xerostomia.

**Methods:** 27 NPC patients treated by intensity modulated radiotherapy in 2018 were recruited. Resting saliva flow rates of individual saliva gland including parotid and submandibular glands were measured before radiotherapy, at 6-month, 12-month and 18-month post-radiotherapy (post-RT). At the same time points, patients' feedback on the severity of xerostomia was obtained from a validated questionnaire. Trend lines of the saliva flow rate and questionnaire scores were plotted, and the correlations of salivary gland doses and the percentage change of saliva flow rate at the time of greatest impact were also investigated.

**Results:** Similar doses were received by the parotid gland and submandibular gland. The saliva flow rates of the parotid gland and submandibular gland showed significant decrease of over 80% at 6 months post-RT and stayed at similar low level thereafter. There was no significant correlation between post-RT saliva flow rate changes and mean doses received by the glands. For the xerostomia questionnaire scores, the feelings of dryness and comfortability of mouth deteriorated significantly at 6 months post-RT. Great impacts of xerostomia on sleeping, speaking, eating and wearing dentures were also observed at 6 months post-RT and they remained fairly constant afterward.

**Conclusion:** The average mean doses to parotid and submandibular glands were around 35 Gy in IMRT of NPC patients, which significantly reduced the saliva flow rates of the parotid and submandibular glands. The impact was greatest at 6 months post-RT and was long lasting. Patients' quality of life was affected by the severity of xerostomia and the effects showed similar pattern as the saliva flow rates.

**Keywords:** Saliva flow rate • Xerostomia • Radiotherapy • Nasopharyngeal carcinoma • Radiation-induced changes

**Abbreviations:** CT: Computed Tomography; $D_{max}$: Maximum Dose; $D_{mean}$: Mean Dose; $D_{min}$: Minimum Dose; DVH: Dose Volume Histogram; Gy: Gray; IMRT: Intensity Modulated Radiotherapy; MV: Mega Voltage; NPC: Nasopharyngeal Carcinoma; PTV: Planning Target Volume; RT: Radiotherapy; SD: Standard Deviation

## Introduction

Xerostomia is one of the common side effects in radiotherapy (RT) of nasopharyngeal cancer (NPC) patients [1,2]. Xerostomia causes difficulties in mastication and swallowing and enhances the risks of dental problems, which subsequently degrade the quality of life in the long-term survivors [3,4]. The cause of xerostomia is mainly due to the damage of the parotid and submandibular glands, which are the major salivary glands that produce over 80% of saliva [5]. Since both the parotid and submandibular glands are located close to the target volume of NPC, portions of them are inevitably irradiated to high dose. Despite some studies have reported that there was recovery of the salivary gland after radiotherapy, it was not a complete restoration of the normal saliva production in the NPC patients and the post-radiotherapy (post-RT) impact on the glands was long lasting [6]. Nevertheless, studies on radiotherapy in head and neck cancer patients reported that mean dose of less than 25-30 Gy to the parotid gland could allow saliva flow rate recovery [7,8].

Dry mouth is the subjective feeling of the patients with xerostomia, and it is expected to be closely related to the salivary flow rate [9]. When the stimulated salivary flow rate is ≤ 0.7 $cm^3$/minute or the unstimulated salivary flow rate is ≤ 0.1 $cm^3$/minute, it is regarded as hyposalivation [10,11], which is the main feature of xerostomia. Since the major salivary glands are irradiated in different extents in a radiotherapy course for NPC patients, it is useful to study the saliva production of the two main salivary glands by measuring salivary flow rates from multiple sites, including the Stenson duct opening for the parotid gland and the Wharton duct opening for submandibular glands [12].

With regard to the radiotherapy of NPC patients, this longitudinal study aimed to evaluate the post-radiotherapy changes of salivary flow rates in the major salivary glands and the severity of xerostomia collected through a validated questionnaire based on patients' subjective experience. In addition, the associations between the change of saliva flow rate and mean radiation dose received by the major salivary glands were also studied.

## Material and Methods

Twenty-seven NPC patients (age range: 29-66, median age: 53) treated

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with intensity modulated radiotherapy (IMRT) between April to December 2017 were recruited. The patient characteristics are shown in Table 1. Written informed consent was obtained from the patients to join the study before the start of the treatment. Ethics approval was obtained from the Research Ethics Committee of the Hong Kong Polytechnic University and from Institutional Research Board of the University of Hong Kong. Each patient underwent planning computed tomography (CT) of the head and neck region. The CT data were transferred to radiotherapy treatment planning system (Eclipse™, Varian Medical Systems, Palo Alto, CA) where the IMRT plans were generated. The routine IMRT plan for NPC consisted of nine equally spaced 6 MV photon beams covering the base of skull down to the lower neck. The planning target volumes (PTV) of the nasopharynx and neck lymphatics were prescribed with 70 Gy and 66 Gy respectively. Dose parameters of parotid and submandibular glands including maximum dose ($D_{max}$), minimum dose ($D_{min}$) and mean dose ($D_{mean}$) were obtained from their respective dose volume histograms (DVHs) generated from the treatment planning system.

Unstimulated saliva flow rates of parotid gland and sub-mandibular glands were measured by placing a cotton swab at the salivary duct orifices. They included the left and right orifices of the Stenson duct, which was located between parotid papilla and maxillary second molar for the parotid gland, and the Wharton duct orifice at the floor of mouth for the sub-mandibular gland. To collect the saliva, the patients were advised not to eat one hour before the collection time. Mouth rinsing with distilled water was done 10 minutes before collection. A polypropylene vial with a cotton swab was pre-weighed before placing the cotton swab at the collection sites. This was conducted one at a time and repeated for other sites. Then a collection time of five minutes was set using a timer. At the end of collection, the cotton swab was removed from the site and re-weighed. The saliva flow rate ($cm^3$/minute) was calculated by the difference of post-collection and pre-collection cotton swab mass divided by the duration of saliva collection (5 minutes). The measurement of saliva flow rate was performed before radiotherapy (pre-RT), and at 6, 12 and 18 months after completion of RT.

To survey the subjective xerostomia condition in the patients, the patients were required to complete a structured and validated xerostomia questionnaire adopted from Zimmerman et al. [13] at each time interval (i.e. pre-RT, 6, 12 and 18 months post-RT). The questionnaire consisted of six questions on the severity of xerostomia according to its impact on the patient's daily life including (1) Difficulty in swallowing and mastication; (2) Difficulty in speech; (3) Interruption of sleep; (4) Discomfort of mouth; (5) Dryness of mouth and (6) Difficulty in wearing denture, if any (Table 2). A continuous scale from 0-1.0 was used to assess the severity of xerostomia. A score of 0 representing there was maximum distress or difficulty experienced and a score of 1.0 representing there was no distress or difficulty experienced [6].

Trend lines were plotted to assess the change of saliva flow rates of individual glands, and the scores of each question in the xerostomia questionnaire as mean ± standard deviation (SD). The difference of saliva flow rates and questionnaire scores over two consecutive time intervals was analyzed by paired t-test. The correlations between percentage changes of saliva flow rates with the mean gland doses at the time point with greatest impact were analyzed using the Pearson correlation test. Statistical Product and Service Solutions (SPSS) version 22 was used for statistical analyses.

## Results

All patients completed the radiotherapy uneventfully. Similar doses were received by the parotid gland and submandibular gland, with the average maximum dose over 70 Gy and mean dose around 35 Gy (Table 3). The saliva flow rate of the parotid gland showed significant decrease from pre-RT (0.32 $cm^3$/minute) to 6 months post-RT (0.01 $cm^3$/minute) and stayed at similar low level thereafter (Figure 1). The overall mean parotid saliva flow rate reduction was around 81%. Similarly, the saliva flow rate of the submandibular gland decreased significantly from pre-RT (0.43 $cm^3$/minute) to 6 months post-RT (0.03 $cm^3$/minute) and stayed at similar low level thereafter (Figure 2). The overall mean parotid saliva flow rate reduction was around 85%. The greatest impact was reported at 6 months after radiotherapy where the percentage reduction was the steepest. At this time point, there was no significant correlation between post-RT saliva flow rate changes and mean doses received by the glands as illustrated by the Pearson correlation coefficient (r=0.153 and 0.097 for parotid and submandibular glands respectively) and scatter plots (Figures 3 and 4).

With regard to the xerostomia questionnaire scores, the feelings of dryness

**Table 1.** Patient characteristics (n=27).

| Variables | | Number of Patients (%) |
|---|---|---|
| Gender | Male | 17 (62.9%) |
| | Female | 10 (37.0%) |
| Tumor Stage (AJCC) | I | 3 (11.1%) |
| | II | 5 (18.5%) |
| | III | 9 (33.3%) |
| | IV | 8 (29.6%) |
| | Unknown | 2 (7.4%) |
| Chemotherapy | Yes | 21 (77.8%) |
| | No | 4 (14.8%) |
| | Unknown | 2 (7.4%) |

AJCC: American Joint Committee on Cancer

**Table 2.** Xerostomia questionnaire.

| Questions | Response Score* (100 mm horizontal scale) |
|---|---|
| 1. During the last 3 days, overall, your mouth or tongue was: | Very dry (0) – Not dry (1) |
| 2. In general, during the daytime hours of the last 3 days, the feeling of your mouth and tongue was: | Extremely uncomfortable (0) – Comfortable (1) |
| 3. During the last 3 nights, due to the dryness of your mouth and tongue, how difficult was it to sleep? | Very difficult (0) – Easy (1) |
| 4. During the last 3 days, overall, due to the dryness of your mouth and tongue, how difficult was it to speak without drinking fluid? | Very difficult (0) – Easy (1) |
| 5. During the last 3 days, overall, due to the dryness of your mouth and tongue, how difficult was it to chew and swallow food? | Very difficult (0) – Easy (1) |
| 6. If you normally wear dentures; due to the dryness of your mouth and tongue, how difficult was it to wear dentures in the last 3 days? | Very difficult (0) – Easy (1) |

*100 mm score scale was used with a score of 0 representing there was significant distress experienced and a score of 1 representing there was no distress experienced.

**Table 3.** Average doses received by parotid and submandibular glands.

| Variables | Dosage | Mean ± SD |
|---|---|---|
| Parotid gland (n= 54) | $D_{max}$ | 71.1 ± 1.5 Gy |
| | $D_{min}$ | 14.0 ± 2.8 Gy |
| | $D_{mean}$ | 35.9 ± 5.1 Gy |
| Submandibular gland (n= 54) | $D_{max}$ | 70.9 ± 1.8 Gy |
| | $D_{min}$ | 13.5 ± 3.3 Gy |
| | $D_{mean}$ | 34.4 ± 3.7 Gy |

$D_{max}$: Maximum dose; $D_{min}$: Minimum dose; $D_{mean}$: Mean dose; SD: Standard deviation

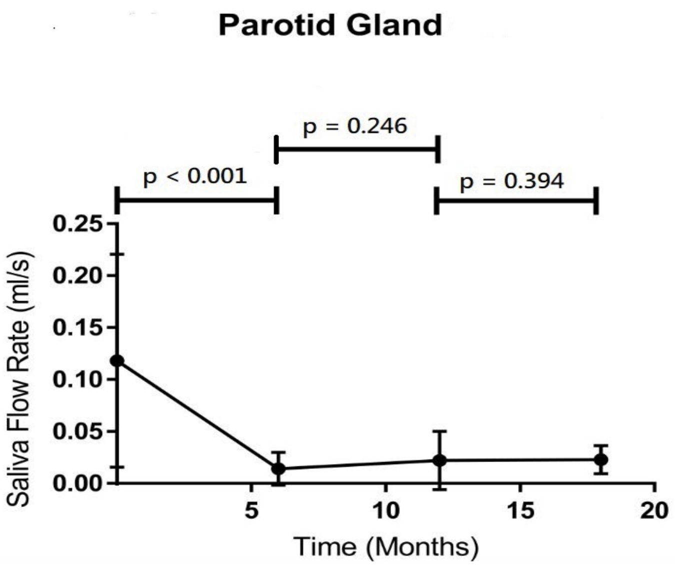


**Figure 1.** Trend line showing average saliva flow rate of the parotid gland from pre-RT to 18 months post-RT. P values of t-test for two consecutive time intervals are stated at the top of the graph.

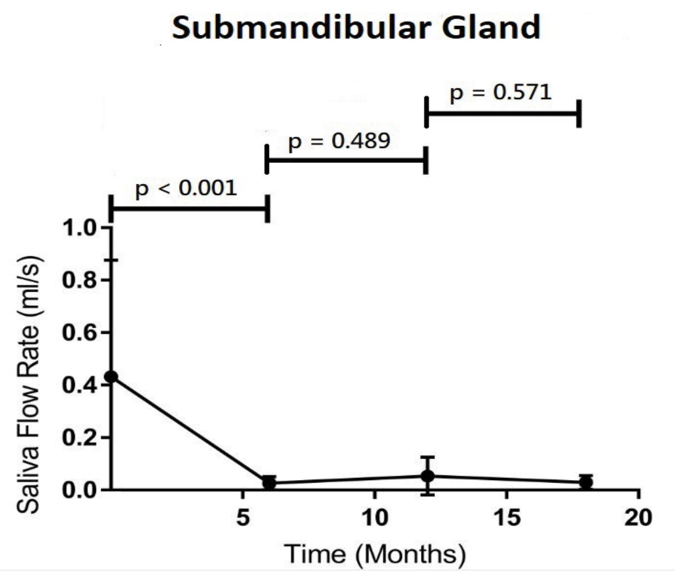


**Figure 2.** Trend line showing average saliva flow rate of the sub-mandibular gland from pre-RT to 18 months post-RT. P values t-test for two consecutive time intervals are stated at the top of the graph.

and comfortability of mouth and tongue (Questions 1 and 2) deteriorated significantly at 6 months post-RT (p<0.001) followed by a slight improvement at 12 months and then remained unchanged at 18 months post-RT (Figures 5A and 5B). For the impact of xerostomia on daily activities including sleeping (Question 3), speaking (Question 4), eating (Question 5) and wearing dentures (Question 6), significant deterioration wasalso found at 6 months post-RT (Figures 5C-5F). Some extent of relieves were observed after 12 months post-

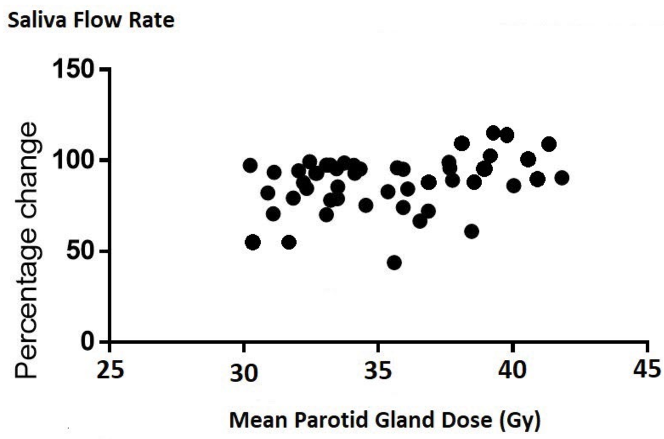


**Figure 3.** Scatter plot showing the relationship between percentage change of saliva flow rate and mean parotid gland dose.

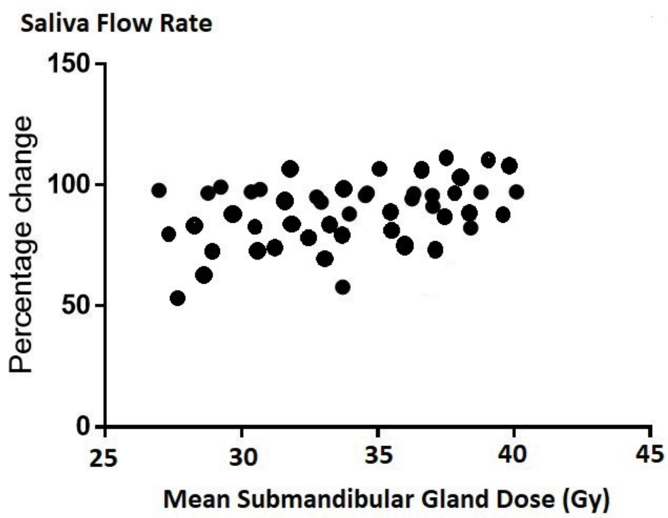


**Figure 4.** Scatter plot showing the relationship between percentage change of saliva flow rate and mean submandibular gland dose.

RT in eating (Figure 5E) and wearing of dentures (Figure 5F) (p=0.048 and 0.037 respectively), while the other activities showed no significant change.

## Discussion

Our study showed that radiotherapy of the current NPC patient cohort using IMRT brought relatively high doses to both parotid glands and submandibular glands (with average mean dose of about 35 Gy) compared with those in other head and neck cancers (average mean dose to parotid of less than 28 Gy) [14]. There was little difference between the maximum and mean doses of parotid gland and submandibular gland, indicating that both glands were situated in similar proximity to the target volume. As the dose tolerance for parotid gland suggested by previous literatures were mean dose of 23-25 Gy [15,16], it was not surprising to see xerostomia developed in this cohort of patients.

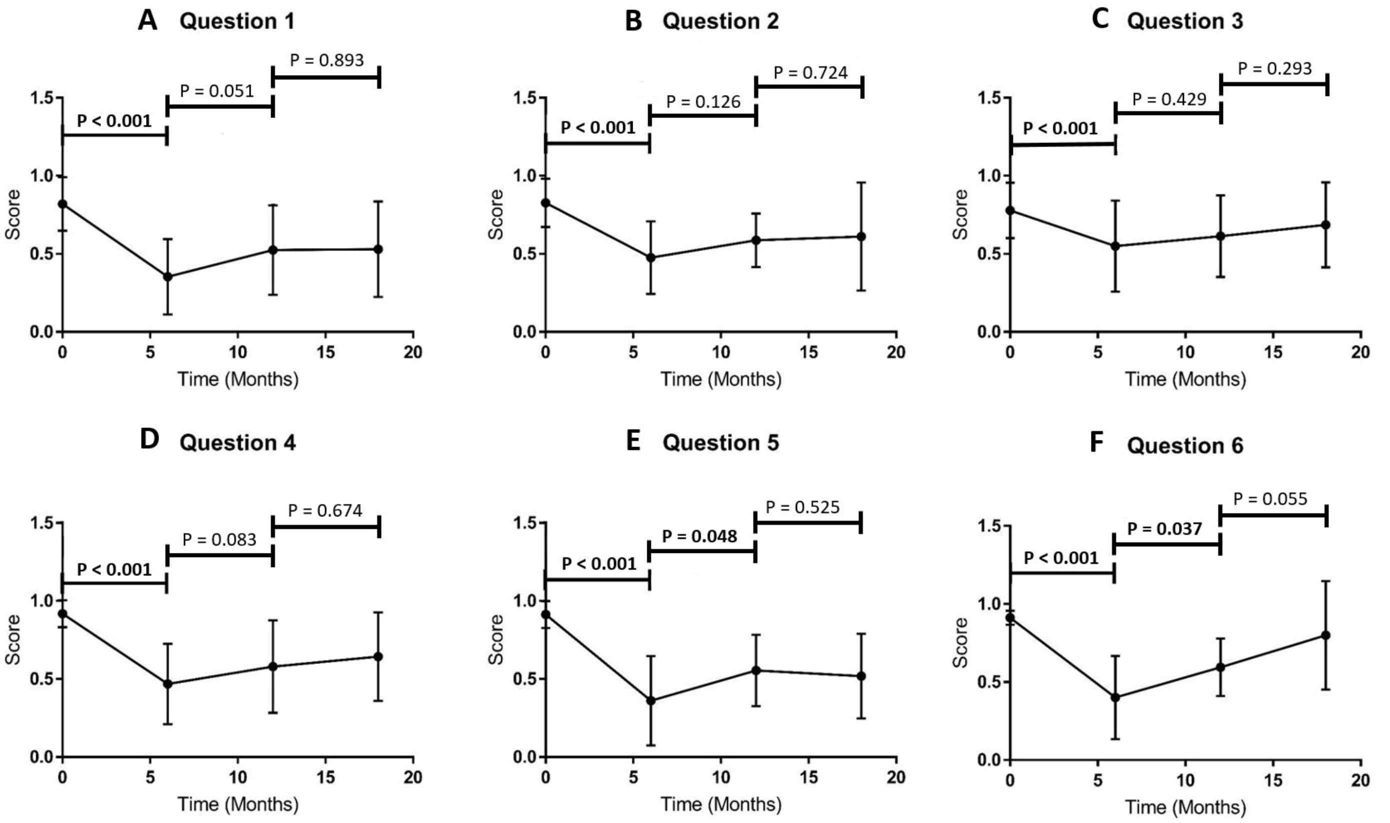


**Figure 5.** Xerostomia questionnaire scores.

Our study demonstrated significant mean saliva flow rate reduction of over 80% in the first 6 months after radiotherapy for both parotid and submandibular glands. The mean flow rates at 6 months post-RT for both glands were less than 0.05 $cm^3$/minute, which was an indication of xerostomia condition. This was in line with Owosho et al. [15] who reported that xerostomia following IMRT peaked within 6 months post-RT. Our results also echoed the study by Sim et al. [17] who demonstrated significant decreases of mean resting saliva flow rates from 0.67 $cm^3$/minute pre-radiotherapy (pre-RT) to 0.10 $cm^3$/minute at 3-month post-RT. Our study showed that the reduction trend tailed off after the 6 month interval and the mean flow rate remained relatively constant up to 18 months post-RT. This implied that with no intervention to this cohort of patients, xerostomia persisted up 18 months after completion of radiotherapy. Although a previous study reported partial recovery of the salivary function in post-RT head and neck cancer patients [18], this was not observed in our patient cohort. The reasons could be twofold: 1) That study was on head and neck cancers and its mean parotid dose was lower than our study and 2) That study covered a longer follow up time of over two years. Our study was a stage one study that collected data up to 18 months post-RT, continuous follow up on these patients are underway which will show if recovery of salivary function afterward. Nevertheless, an important finding in our study was that at the time when there was the greatest reduction of saliva flow rate (6-month post-RT), there was no significant correlation between post-RT saliva flow rate changes and mean doses received by the glands. This could be explained by the fact that majority of the mean doses to the salivary glands (Figures 3 and 4) received by the patients were above the tolerance of the salivary glands (23-25 Gy as mentioned above). Once the tolerance was exceeded, their salivary functions were all affected by similar extent regardless of the magnitude of the mean dose. This echoed the suggestion of keeping the mean salivary gland dose below their tolerance is important to minimize xerostomia [19].

The results of the xerostomia questionnaires showed similar patterns as the saliva flow rate. The steepest reductions in the average scores of all questions were observed at 6 months post-RT, which indicated that the condition of xerostomia was most severe at this time point. This was the time when the patients felt most uncomfortable (Questions 1 and 2) with all the activities including talking, eating and sleeping (Questions 3-5) being seriously affected. These conditions persisted for more than a year despite eating and wearing denture had slightly improved, which could be partly due to self-adaptation with respect to time [18]. Our results proved that the effect of xerostomia was long lasting and the quality of life of the patients was compromised. It was suggested that for patients with mean dose to the salivary gland above 25Gy, prompt actions such as prescription of artificial saliva, acupuncture or hyperbaric oxygen treatment [20] may be given before 6 months post-RT to relieve the distressing symptoms of xerostomia. Continuous follow up of the patients is important to keep a better quality of life.

# Conclusion

In this study, the average mean doses to parotid and submandibular glands were around 35 Gy in IMRT of NPC patients, which significantly reduced the saliva flow rates of the parotid and submandibular glands. The impacts were the greatest at 6 months post-RT and they persisted up to 18 months. Patients' quality of life was seriously affected by the severity of xerostomia.

# Declarations

## Ethics approval

Ethics approval from the Hong Kong Polytechnic University (Reference No: HSEARS20154540002) and University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference No: UW 16-1006).

## Consent for publication

Not applicable

## Availability of data and materials

Materials in the manuscript are available by contacting the author at htvinwu@polyu.edu.hk

## Competing interests

There is no financial or non-financial competing interest for all authors

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## Authors Contributions

Vincent WC Wu: Design of study, collection and analysis of data, final editing and paper submission; Michael TC Ying: Design of study, measurement of data; Dora LW Kwong: Design of study, recruitment of subjects; Pek L Khong: Design of study; Gary KW Wong: Recruitment of subject, measurement of data; Shing Y Tam: Collection and analysis of data, drafting of manuscript.

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