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Long-term outcomes of stimulated salivary flow and xerostomia after definitive intensity-modulated radiation therapy for patients with head and neck cancer†

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ABSTRACT

This retrospective study aimed to evaluate the time to recovery from xerostomia and analyze its predictors, along with long-term outcomes of stimulated salivary flow after intensity-modulated radiation therapy (IMRT) for head and neck cancer (HNC). We evaluated patients with HNC who had received IMRT with curative intent between 2012 and 2018 at our institution. The salivary recovery ratio (SRR) was defined as '(the stimulated salivary flow)/(pre-treatment salivary flow)'. The cutoff value of SRR in salivary recovery was estimated via the relationship between SRR and xerostomia grades. The salivary recovery time was defined as the time for SRR to exceed cutoff values from the end of radiotherapy. Fifty-seven patients were analyzed, with a 48-month median follow-up period of stimulated salivary flow. The cutoff value for SRR was 44.8%, and patients with a higher grade of xerostomia had a lower SRR ($P < 0.001$). The median salivary recovery time was 12 months. The cumulative incidence rates of salivary recovery at two and four years were 84 (95% confidence interval [CI]: 53–79) and 92% (95% CI: 82–97), respectively, and these were significantly lower in patients with a higher mean parotid gland dose, mean oral cavity dose and stimulated salivary flow per parotid gland volume. Stimulated salivary flow and xerostomia recover over a long period after radiotherapy.

Keywords: xerostomia; stimulated salivary flow; Saxon test; intensity-modulated radiation therapy; volumetric modulated arc therapy

INTRODUCTION

Head and neck cancer (HNC) is a severe disease that affects the vital organs involved in eating, talking and breathing, thereby reducing patients' quality of life (QOL) [1]. Therefore, the treatment strategy for HNC requires managing tumors while ensuring minimal loss of a patient's QOL. Radiotherapy is one of the most important treatment modalities that provide organ preservation for HNC [2, 3]. However, radiation-induced adverse events reduce patients' QOL in the acute and late phases of radiotherapy. Notably, xerostomia is one of the most significant adverse events that can severely reduce the QOL of a patient with HNC over a long period of time [4].

Intensity-modulated radiation therapy (IMRT) has reduced the incidence of xerostomia compared to conventional radiation therapy, thus significantly improving the QOL of patients with HNC [5]. However, most patients treated with IMRT experience temporary severe xerostomia, which requires several years of recovery [6]. Although differences in the recovery time of xerostomia have been observed among patients, limited reports indicate individual differences in the

recovery time. This study thus aimed to evaluate the salivary recovery time after IMRT for HNC.

MATERIALS AND METHODS

Study population

We retrospectively investigated patients with HNC who received radiotherapy between January 2012 and December 2018 at our institution to evaluate the time for recovery from xerostomia and analyze its predictors, along with long-term outcomes of stimulated salivary flow after IMRT for HNC. The inclusion criteria were (i) IMRT, including volumetric modulated arc therapy (VMAT) for curative intent, (ii) bilateral neck irradiation and (iii) salivary flow measurement before radiotherapy. The exclusion criteria were (i) any surgery for HNC before radiotherapy except for surgical biopsy, (ii) no salivary flow measurement one to six months after radiotherapy and (iii) no salivary flow measurement $\geq$18 months after radiotherapy; these exclusion criteria were established to evaluate the long-term salivary flow accurately.

Treatment

All patients were immobilized in a supine position using a head mask. Computed tomography (CT) scans were performed from head to chest. The gross tumor volume (GTV) was defined as primary tumor and lymph node metastasis identified by CT, magnetic resonance imaging, fluorodeoxyglucose-positron emission tomography and fiberoptic endoscopic findings. Clinical target volume (CTV) 70 was the area of GTV plus a margin of 5–20 mm to consider micro invasion. CTV 63 included the area of pharyngeal and laryngeal mucosa where GTV 70 was present and the high-risk lymph node area. CTV 56 included the low-risk lymph node area. Planning target volume (PTV) was defined as each CTV plus a 5-mm setup margin. Before May 2015, seven-field step-and-shoot IMRT was administered. After May 2015, VMAT was administered. Both IMRT and VMAT were delivered with four or six MV flattened photon beams generated by Clinac 6EX, Clinac iX or TrueBeam (Varian Medical Systems, Washington DC, USA). The simultaneous integrated boost technique was used to deliver 70, 63 and 56 Gy in PTV 70, PTV 63 and PTV 56 in 35 fractions, respectively.

Concurrent chemotherapy was administered to patients except for early stage or elderly patients. Moreover, induction chemotherapy was administered to selected patients in locally advanced stages. In principle, the tri-weekly cisplatin regimen was selected for concurrent chemotherapy, and the docetaxel-cisplatin-5-FU regimen was selected for induction chemotherapy. Adjuvant chemotherapy was not administered routinely.

Contouring organs at risk and dose–volume histogram analysis

The parotid glands, oral cavity and submandibular glands were defined as the organs at risk (OARs) involved in radiation-induced xerostomia. They were reviewed and recontoured as necessary according to consensus guidelines [7] by a radiation oncologist specializing in HNC (S.H.) in the planning system (Eclipse 16.01.10) for this study. All treatment plans were recalculated, and the volume and median dose for OARs were evaluated on the dose–volume histograms.

For optimization, the contralateral parotid gland was targeted to have V30 Gy <40% and a mean dose of <30 Gy. The oral cavity was targeted to have a mean dose of <40 Gy. The ipsilateral parotid gland dose was also reduced without loss of target coverage. When the submandibular gland was located outside the PTV, it was targeted to have a mean dose of <40 Gy.

Measurement of stimulated salivary flow

The Saxon test is used to measure the amount of stimulated salivary flow by chewing a 7.5 cm × 10 cm gauze folded in half in the mouth for 2 min [8]. The method allows for the convenient evaluation of stimulated salivary flow and finds application in the diagnosis of Sjogren's syndrome [9]. We perform the Saxon test for patients with HNC as a routine clinical assessment in the radiation oncology clinic at our institution. Generally, the Saxon test is periodically administered before radiotherapy and at 3-month intervals from 1 to 60 months after radiotherapy. Therefore, stimulated salivary flow was measured in all patients included in this study using the Saxon test. Furthermore, xerostomia was graded with the Common Terminology Criteria for Adverse Events version 4.0; Grade 1, symptomatic without significant dietary alteration; Grade 2, moderate symptoms, oral intake alterations and Grade 3, inability to adequately aliment orally. The volume density of stimulated salivary flow was defined as the stimulated salivary flow divided by the sum of left and right parotid gland volume before radiotherapy.

Definition of the salivary recovery time

The salivary recovery ratio (SRR) at measurement was defined as '(stimulated salivary flow at measurement) / (pre-treatment salivary flow)'. Receiver operating characteristic (ROC) curves were created to define a cutoff value for SRR in xerostomia recovered to Grade $\leq$ 1. The salivary recovery time was defined as the time for SRR to exceed the cutoff value from the end of radiotherapy. The cumulative incidence rate of salivary recovery was defined as the percentage of patients whose SRR exceeded the cutoff value.

Statistical analysis

Patients were divided into two groups for each explanatory variable, including mean parotid gland dose, mean oral cavity dose, mean submandibular gland dose, volume density of stimulated salivary flow, pre-treatment salivary flow, parotid gland volume, age, sex and chemotherapy status. Except for sex and chemotherapy status, the median values were used as thresholds for dividing the two groups. The difference between contralateral and ipsilateral parotid gland dose was evaluated using the Mann–Whitney U test. The correlation between pre-treatment salivary flow and parotid gland volume was evaluated using Spearman's rank correlation coefficient. The cumulative incidence rate of salivary recovery was compared using the Fine and Gray model between the two groups. To further examine the relationship between xerostomia and stimulated salivary flow, the difference in SRR between each xerostomia grade was analyzed at 24 months after radiotherapy using a one-way analysis of variance, followed by pairwise *t*-test using the Bonferroni correction. All statistical analyses were conducted with EZR (Saitama Medical Center, Jichi Medical University, Saitama,

Table 1. Patient characteristics

	n	%
Age (years), median [range]	65 [24–88]	
Sex		
Male	45	78.9%
Female	12	21.1%
Primary site		
Nasopharynx	7	12.3%
Oropharynx	21	36.8%
Hypopharynx	23	40.4%
Larynx	6	10.5%
Pretreatment salivary flow (g), Median [range]	4.3 [1.47–9.97]	
Dose		
70 Gy/35 fr.	53	93.0%
72 Gy/60 fr./bid.	2	3.5%
64 Gy/40 fr./bid.	1	1.8%
60 Gy/30 fr.	1	1.8%
Technique		
IMRT	24	42.1%
VMAT	33	57.9%
Chemotherapy		
Yes	48	84.2%
No	9	15.8%

Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [10]. *P* values <0.05 were considered statistically significant.

RESULTS

Seventy-two patients met the inclusion criteria, of which 15 met the exclusion criteria. Therefore, the final analysis was performed on 57 patients. Patient characteristics are shown in Table 1. No patients complained of xerostomia before radiotherapy.

The median volume density of stimulated salivary flow, pretreatment salivary flow and parotid gland volume were 0.084 g/cm^3 (0.024–0.21), 4.3 g (1.47–9.97) and 53 cm^3 (22–126.5), respectively. No significant correlation was observed between the pretreatment salivary flow and parotid gland volume ($r = 0.124$; $P = 0.36$). The median values of the mean dose for the parotid glands, contralateral parotid gland, ipsilateral parotid gland, oral cavity and submandibular glands were 32 (15.3–51.0), 29 (12.7–47.8), 33.6 (17.6–70), 45 (12.2–65.2) and 64 (41.5–72.9) Gy, respectively. A significant difference was found in the mean dose for the contralateral and ipsilateral parotid glands ($P < 0.01$).

The median follow-up period of stimulated salivary flow was 48 months (18–60). The lowest SRR was recorded approximately 3 months after radiotherapy; however, it improved gradually over several years. The percentages of each xerostomia grade at 6, 12, 24 and 48 months after radiation therapy are shown in Fig. 1. The ROC curves indicated that the cutoff value for SRR was 41.8%, and the area under the curve was 0.79 (95% confidence interval [CI]: 0.71–0.87) (Fig. 2). Patients with higher grades of xerostomia had a lower SRR ($P < 0.001$) at 24 months after radiotherapy (Fig. 3). The median salivary recovery time was 12 months. The cumulative incidence rate of salivary recovery at 2 and 4 years was 84% (95% CI: 53–79) and 92% (95% CI: 82–97), respectively.

The cumulative incidence rate of salivary recovery was significantly lower in patients with higher mean parotid gland dose, contralateral parotid gland dose, ipsilateral parotid gland dose, mean oral cavity dose and volume density of stimulated salivary flow. Age, sex, chemotherapy status, mean submandibular gland dose, parotid gland volume and pretreatment salivary flow were not significant factors (Fig. 4, Table 2).

DISCUSSION

Our study evaluated changes in stimulated salivary flow in a long-term follow-up for patients with HNC who were administered definitive IMRT. We obtained two important clinical findings. First, the stimulated salivary flow gradually recovered over a long period after radiotherapy and was associated with xerostomia recovery. Second, patients with a higher mean parotid gland dose, mean oral cavity dose and volume density of stimulated salivary flow experienced a slower recovery of stimulated salivary flow.

Long-term data are indispensable for analyzing the recovery of xerostomia after radiotherapy for HNC. Limited reports have analyzed comparable or larger long-term data; these reports evaluated QOL scores or salivary gland scintigraphy without measuring salivary flow over long durations [3, 11–17]. Thus, to our knowledge, our study is the first to measure the stimulated salivary flow over a long period following radiotherapy for HNC.

Our long-term examination of stimulated salivary flow and xerostomia suggests that there was a gradual improvement in salivary flow and xerostomia recovery in the 5 years following radiotherapy. Furthermore, the recovery of stimulated salivary flow was related to that of xerostomia after radiotherapy. Although with a shorter follow-up time of 1–2 years, previous reports have also shown a correlation between stimulated salivary flow and xerostomia [18, 19].

The tools to evaluate xerostomia include the stimulated salivary flow, the salivary gland scintigraphy and patient-reported outcomes (PROs). All of the tools allow for quantitative evaluation. PROs can get the subjective evaluation because patients assess their symptoms themselves; several reports indicated that PROs were vital for assessing patients' subjective symptoms. These reports suggested that PROs were strongly associated with parotid gland dosimetry and were easy to record [20, 21]. However, generating PROs is time-consuming as patients need to answer numerous questions, so minimizing the time burden when using PROs is recommended [22]. Salivary gland scintigraphy can assess the function of each salivary gland; however, it is time-consuming and involves radiation exposure [23]. In contrast, the Saxon test can evaluate the function of salivary glands inexpensively without radiation exposure; in addition, it is likely easier and faster to perform than the examination of PROs. This is because we selected the Saxon test in routine clinical practice as a surrogate parameter for xerostomia to evaluate changes in xerostomia over time. Our results suggest that stimulated salivary flow measured by the Saxon test is useful as a surrogate marker for xerostomia in routine practice after

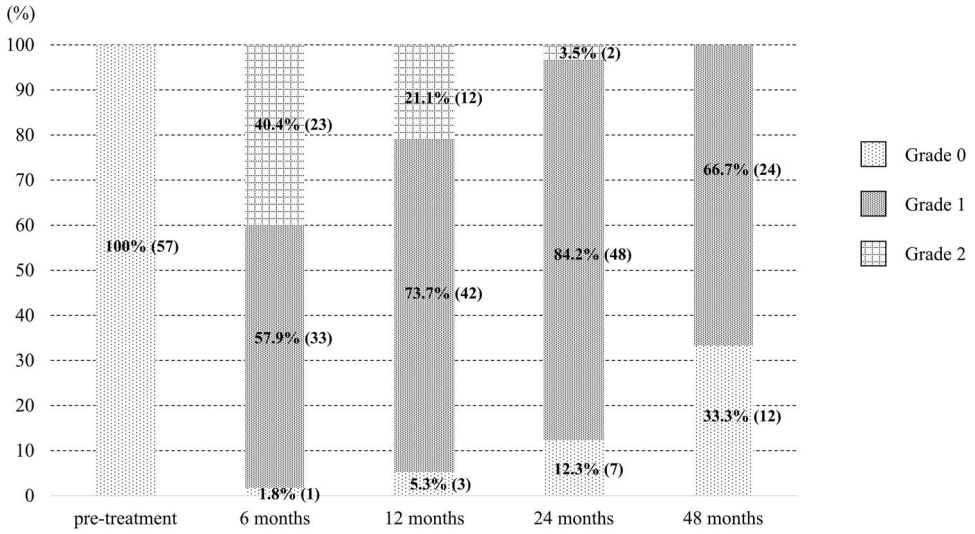

Fig. 1. Percentage and number of patients in xerostomia grade at each time point.

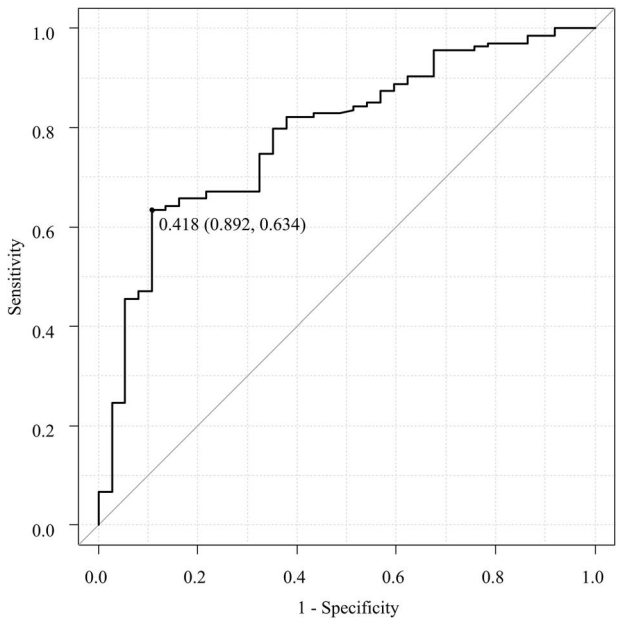

Fig. 2. ROC curves for SRR.

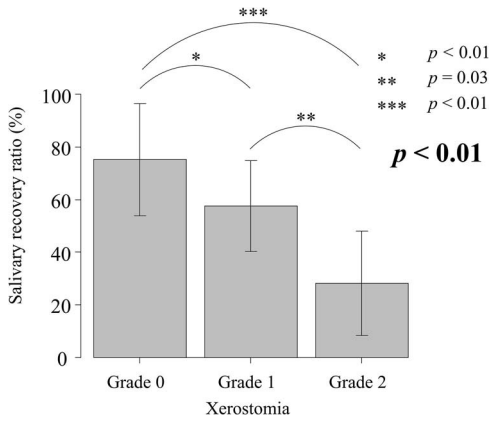

Fig. 3. Difference in SRR between each xerostomia grade after radiotherapy.

radiotherapy for HNC. Additionally, patients often feel anxious about when they will recover from xerostomia because xerostomia persists for a long period. Our results may provide each patient with an estimated recovery period of xerostomia before radiotherapy, and a better understanding of recovering xerostomia.

Furthermore, we applied SRR instead of the absolute salivary flow as a recovery index for xerostomia to evaluate the relative change in subjective symptoms over time for each patient. The absolute salivary flow is unreliable for evaluation because it is difficult to evaluate patients with low pretreatment salivary flow who have achieved recovery of salivary flow even with improvement in their xerostomia. Moreover, patients with high pretreatment salivary flow may be misjudged as having recovered from xerostomia if their salivary flow remains high despite subjective symptoms. However, the SRR allows us to evaluate the change from baseline regardless of the pretreatment salivary flow. Several reports have evaluated xerostomia using SRR, reflecting the Grade 4 parotid gland toxicity, defined as SRR ≤25% at the RTOG/EORTC Late Effects Consensus Conference [24–26].

Our findings revealed that patients with higher mean parotid gland dose, mean oral dose and volume density of stimulated salivary flow experienced a slower recovery of stimulated salivary flow. The parotid gland mean dose correlates with the xerostomia severity, and the dose reductions have been recommended [6, 27]. Parotid glands produce most of the stimulated salivary flow, and the dose reduction of parotid glands was proven to improve xerostomia in a randomized controlled trial [5, 26]. Additionally, minor salivary glands are present in the oral cavity and produce most mucins in saliva. Mucins bind water molecules and maintain a hydrated state, contributing to the patient's sense of hydration [28]. The importance of oral cavity dose was also reported by Cao *et al.*, and oral cavity dose was correlated with late xerostomia

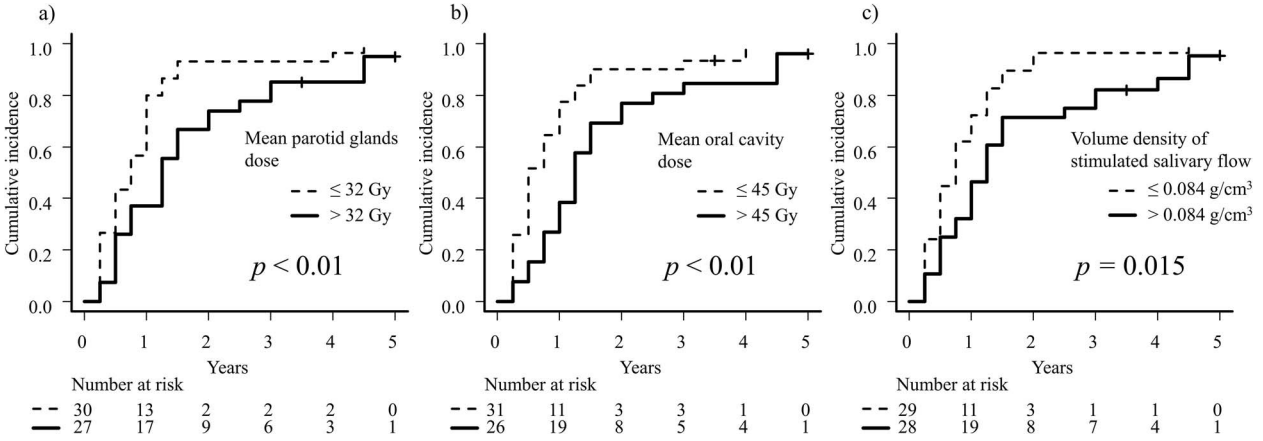

Fig. 4. Curves of the cumulative incidence rate of salivary recovery compared to (a) the mean parotid glands dose, (b) the mean oral cavity dose and (c) the volume density of stimulated salivary flow.

Table 2. Comparison of the cumulative incidence rate of salivary recovery between the groups

Variable	*P* value	HR (95% CI)
Age (≤65 vs >65 years old)	0.72	1.09 (0.69–1.73)
Sex (male vs female)	0.43	1.25 (0.72–2.16)
Chemotherapy (yes vs no)	0.26	0.70 (0.38–1.30)
Mean parotid glands dose (≤32 vs >32 Gy)	<0.01	0.51 (0.31–0.85)
Mean contralateral parotid gland dose (≤29 vs >29 Gy)	0.02	0.56 (0.34–0.91)
Mean ipsilateral parotid glands dose (≤33.6 vs >33.6 Gy)	0.01	0.53 (0.32–0.88)
Mean oral cavity dose (≤45 vs >45 Gy)	<0.01	0.49 (0.30–0.80)
Mean submandibular glands dose (≤64.1 vs >64.1 Gy)	0.33	0.79 (0.49–1.27)
Volume density of stimulated salivary flow (≤0.084 vs >0.084 g/cm^3)	0.02	0.55 (0.34–0.89)
Pretreatment salivary flow (≤4.3 vs >4.3 g)	0.12	0.69 (0.43–1.11)
Parotid gland volume (≤53.0 vs >53.0 cm^3)	0.70	1.10 (0.69–1.76)

[12]. These findings were compatible with the results of our study. On the other hand, there are no previous reports showing that higher volume density of stimulated salivary flow has a slower recovery of stimulated salivary flow. The parotid gland is known to be radiosensitive despite its highly differentiated cells and low turnover rate, which cannot be explained by typical radiosensitive mechanisms. Coppes *et al*. suggested that irradiation selectively damages the plasma membrane in the parotid gland, which negatively affects the modulation of receptor-coupled signaling pathways and may lead to acute injury by severely inhibiting water excretion [29–31]. Thus, patients with a higher volume density of stimulated salivary flow are likely to have activated signaling pathways. As a result, they may be more affected by radiation-induced membrane damage, leading to lower SRR.

This study had a few limitations. First, no patients received unilateral irradiation in our study. The omission of prophylactic irradiation for the contralateral lymph node areas is recommended in some patients with early stage HNC [32]. Moreover, patients who have received unilateral irradiation can produce more saliva after radiotherapy compared to the amount they could produce before radiotherapy due to compensatory changes in the contralateral parotid gland [33]. As no patients received unilateral irradiation in our study and the Saxon test cannot measure left and right salivary functions separately, whether our results are reproducible in patients who receive unilateral irradiation remains unclear. Additionally, the dose difference between the contralateral and ipsilateral parotid glands was observed in our study. Possibly, the function of the contralateral parotid gland was recovered faster than that of the ipsilateral parotid gland; however, we did not have a chance to verify the difference because we performed the Saxon test. Second, it is unclear whether patients achieved satisfactory salivary recovery because we did not evaluate PROs. Third, this was a single-center retrospective study, and our results should be validated by a prospective study.

CONCLUSION

The stimulated salivary flow gradually recovered over a long period of time following IMRT and was associated with the recovery of xerostomia. Parotid glands dose, oral cavity dose and stimulated salivary flow per parotid gland volume were associated with the time to recovery of the stimulated salivary flow. The stimulated salivary flow measured by the Saxon test may be useful as a surrogate marker for xerostomia in routine practice after radiotherapy for HNC.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Informed consent was waived, and the study was approved by the ethics committee of Kyoto University Graduate School and Faculty of Medicine (R1048).

DATA AVAILABILITY

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

AUTHORS' CONTRIBUTIONS

Study conception and design: S.H., M.Y. and A.N. Material preparation, data collection and analysis: S.H., M.Y., A.N. and R.N. The first draft of the manuscript was written by S.H., and all authors commented on previous versions of the manuscript. All authors read and approved the final.

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