

Physical Function and Quality of Life across Cachexia Stages in Patients with Head and Neck Cancer: A Cross-sectional Study

BINDYA SHARMA¹, TWINKLE YOGESH DABHOLKAR², YOGESH GURUDAS DABHOLKAR³



ABSTRACT

Introduction: Cachexia is a complex syndrome marked by progressive loss of muscle and fat, leading to functional decline and reduced Quality of Life (QoL). The impact of cachexia in Head and Neck Cancer (HNC) remains an underexplored area. They are particularly vulnerable because of swallowing difficulties and early weight loss, which predispose them to cachexia even at diagnosis. Since conventional measures such as skeletal muscle mass are not routinely practiced, there is a need to identify simple, clinically feasible markers of functional impairment.

Aim: To explore physical function like Handgrip Strength (HGS), Six-Minute Walk Distance (6MWD), physical activity using International Physical Activity Questionnaire- Short Form (IPAQ-SF) and QoL using Functional Assessment of Anorexia and Cachexia Therapy (FAACT) across cachexia stages in HNC patients.

Materials and Methods: A cross-sectional analysis was conducted among 32 newly diagnosed HNC patients between March 2023 and March 2024 at Dr. D. Y. Patil University Hospital, Navi Mumbai, Maharashtra, India. Cachexia staging

was performed using the CASC-IN tool, which integrates weight loss, symptom burden, and C-Reactive Protein (CRP) levels. Functional assessments included HGS, 6MWD, IPAQSF, and FAACT. Data were analysed using Oneway Analysis of Variance (ANOVA), posthoc tests, and effect sizes were calculated.

Results: Patients with cachexia showed markedly lower HGS (28.43±2.86 lbs) compared with non cachectic (40.43±7.81 lbs) and precachectic (33.3±5.43 lbs) groups, with a large effect size ($\eta^2=0.48$). No significant differences were observed in 6MWD (393-404 m). Physical activity was lowest in precachexia (115.62±59.36 METs), intermediate in cachexia (224.31±170.02 METs), and highest in non cachexia (344.55±232.05 METs). QoL scores were substantially reduced in both cachectic (53.61±14.79) and precachectic (51.69±7.71) groups compared with non cachectic patients (70.33±11.12).

Conclusion: The HGS emerged as the most sensitive marker of cachexia related muscle dysfunction, while declines in QoL and physical activity were evident even in precachexia. This study demonstrated that each stage of cachexia had different physical functional characteristics in HNC patients and early intervention can prevent functional decline.

Keywords: Exercise tolerance, Head and neck neoplasms, Muscle strength, Physical activity

INTRODUCTION

Cachexia is a multifactorial syndrome characterised by progressive skeletal muscle loss, often accompanied by fat loss that cannot be reversed by conventional nutritional support and leads to functional decline and reduced QoL [1]. India carries the world's heaviest burden of head and neck cancers, accounting for about one-third of global cases, with over 200,000 new diagnoses reported each year [2]. Although extensively studied in other cancers, cachexia remains underexplored in HNC, where it is found to be highly prevalent, affecting approximately 31-42% of patients [3], and may occur early due to the tumour location and symptoms such as dysphagia, leading to significant weight loss at diagnosis [4].

The classification of cachexia identifies three stages; precachexia, cachexia, and refractory cachexia with each stage having some distinct clinical and metabolic features [5,6]. Identification of cachexia stage at baseline may help explain the variability seen in physical and functional outcomes and response to therapeutic interventions [7]. However, clinical assessment remains limited due to the lack of practical and standardised staging systems [8]. The CASC-IN tool addresses this gap by providing a simple, valid, and feasible method to classify cachexia stages without requiring complex and costly assessments [8].

While CASC-IN enables stage classification, functional measures are needed to capture the impact of cachexia. Although reduced

muscle mass and poorer physical function have been observed in cachectic HNC patients, increasing evidence suggests that muscle mass does not directly correlate with functional capacity [9,10]. Since functional decline is a defining feature of cachexia, there is a need for stage-specific evaluation of functional impairment. However, the absence of standardised criteria to define and measure functional impairment remains a major barrier to advancing effective therapies [11,12]. Objective measures such as HGS, which reflects muscle strength and is responsive to interventions, and gait-based assessments like 6MWT, which captures functional capacity and endurance, provide complementary insights into physical function [9,13,14]. Additionally, subjective measures such as the IPAQ-SF and the FAACT offer valuable patient-reported perspectives on physical activity and QoL in cachexia patients [15,16].

Importantly, there are no established criteria to define functional impairment at a single time point, particularly when comparing patients with and without cachexia. Assessing functional parameters at baseline in newly diagnosed patients awaiting medical treatment, allows identification of early functional deficits attributable to primary cachexia, without the confounding effects of treatment [12]. This investigation was conducted as a sub-study within an ongoing cross-sectional project examining the prevalence of cancer cachexia in patients with HNC.

It was hypothesised that cachexia is present at the pretreatment stage in a subset of newly diagnosed HNC patients and that stage-specific differences in physical function can be identified. This study aimed to classify cachexia using CASC-IN and compare stage-specific differences in objective functional measures of HGS and 6MWD and subjective outcomes using IPAQ-SF and FAACT in patients with HNC.

MATERIALS AND METHODS

This was a cross-sectional study conducted on newly diagnosed patients with HNC and awaiting medical/surgical management. The patients admitted to the Primary Healthcare Centre of Dr. D. Y. Patil University Hospital, Navi Mumbai, Maharashtra, India were recruited between March 2023 and March 2024. The study was approved by the Institutional Ethics Committee of Biomedical and Health Research, Dr. DY Patil School of Medicine, Navi-Mumbai (IEC Ref. No: DYP/IECBH/2020/41).

Inclusion criteria: Adult patients between the age of 18-50 years, with histologically confirmed primary squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx who were awaiting treatment with radiotherapy alone or in combination with chemotherapy or surgery were included in the study.

Exclusion criteria: Patients with secondary or metastatic tumours, those on liquid diet or tube feeding, individuals with co-morbidities such as uncontrolled diabetes, liver, kidney, cardiac disease, or COPD, and those with cognitive disorders were excluded to avoid confounding causes of cachexia.

Sampling and participation: A consecutive sampling method was employed, wherein all eligible patients with newly diagnosed HNC admitted during the study period were approached and recruited. The sample population was derived from an ongoing larger cross-sectional study on prevalence of cancer cachexia in HNC and included only patients who provided written informed consent and were clinically fit to complete functional assessments. As participation required both willingness and feasibility, the number of patients in each subgroup was not predetermined and this approach reflected the natural distribution of cachexia status observed in actual clinical population. The study included 32 participants divided into cachectic (n=13), non cachectic (n=11), and precachectic (n=8) groups.

Study Procedure

After informed consent, demographic data like age, gender, height, and weight loss percentage in the past six months were collected. Clinical data included cancer site and stage, CRP levels and Eastern Cooperative Oncology Group (ECOG) Performance Status score. The ECOG is a clinical scale that assesses how cancer affects daily functioning, guiding treatment decisions, trial eligibility, and prognosis through a quick measure of functional status and QoL [17].

Cachexia staging: Patients were classified into stages of cachexia using the CASC-IN tool based on weight loss history, anorexia, self-reported questionnaire scores, and CRP levels [8]. Patients were classified as non cachectic in the absence of weight loss $\leq 5\%$ and negative questionnaire results. In cases where weight loss was $\leq 5\%$ but the questionnaire was positive, CRP levels were used to further determine cachexia stage. Specifically, patients with CRP levels below 5 mg/dL were considered non cachectic, whereas those with CRP levels above 5 mg/dL were classified as precachectic. Patients with $>5\%$ weight loss irrespective of questionnaire findings, were classified as cachectic [8].

As per definition, refractory cachexia is advanced, progressive cancer that is no longer responsive to anticancer treatment, with poor performance status and a life expectancy of less than three months, and where reversal of cachexia is no longer possible [1]. As the cohort comprised newly diagnosed patients, refractory cachexia was not expected.

Outcome variables: The study variables comprised of HGS testing, 6MWD and patient-reported outcomes using the FAACT questionnaire and physical activity using IPAQ. HGS was assessed using a Jamar handheld dynamometer, positioned at the second handle setting, in accordance with the American Society of Hand Therapists (ASHT) recommendations [18]. Measurements were taken on the dominant hand, and the mean of three trials was recorded [19]. Functional capacity was measured using 6MWD administered in accordance with the standardised guidelines established by the American Thoracic Society (ATS) [20]. The QoL was assessed using the FAACT questionnaire based on recall of the past seven days [21,22]. FAACT builds on the Functional Assessment of Cancer Therapy- General (FACT-G), which covers the four core domains (physical, social/family, emotional, functional wellbeing) along with the Anorexia Cachexia Subscale (ACS). The score ranges up to 156, with higher scores indicating better QoL [22]. Physical activity levels were measured by the IPAQ-SF based on recall of the past seven days. It was developed as an instrument for cross-national monitoring of physical activity and inactivity [23]. It has also been found to be a useful indicator of physical activity in cachexia [15]. The short version (9 items) provides information on the time spent walking, in vigorous- and moderate-intensity activity and in sedentary activity along with METS/min values [23].

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 25.0. Descriptive statistics for participant characteristics were represented as mean \pm SD for continuous variables (age, BMI, hand grip strength, 6MWD, IPAQ METs, FAACT score) and as frequencies with percentages for categorical variables (gender, cancer site, stage, ECOG performance status). Normality of the data was tested using the Shapiro-Wilk test, which showed p-value >0.05 for all variables. Since the data were normally distributed and suitable for parametric analysis, One-way ANOVA with Bonferroni post-hoc tests were used to compare functional and quality-of-life parameters across cachexia groups. Effect sizes (eta square) were calculated to determine the magnitude of differences between the groups.

RESULTS

The study included 32 participants divided into cachectic (n=13), non cachectic (n=11), and precachectic (n=8) groups. Patients across the three groups were comparable in age and pre-diagnosis weight. The gender distribution was predominantly male with 87.5% (n=28) and 12.5% (n=4) females. Tongue and transglottic cancers were more frequent in cachectic patients, buccal cancers in non cachectic, and a mixed cancers in precachectic. Advanced stages of III-IV (84.6%) and poorer ECOG scores of 3 (30.8%) were seen in cachectic patients, while non cachectic patients had more Stage II and III (45.5%) disease and better ECOG scores of 1 (63.6%) [Table/Fig-1].

Cachectic patients experienced the greatest absolute weight loss and lowest BMI. When expressed as percentage, weight loss was again highest in cachectic patients, moderate in precachectic, and lowest in non cachectic. Interestingly, CASC-IN scores were elevated in the precachectic group, suggesting that symptom burden and subjective distress may emerge early, even before measurable muscle wasting. Overall, cachexia severity aligned with advanced stage, lower BMI, and poorer ECOG status, while CASC-IN highlighted early clinical impact preceding measurable decline. Weight loss percentage was not compared between groups because it is the defining criterion for cachexia staging. By design, non cachexia, precachexia, and cachexia groups are distinguished by specific weight loss thresholds, making direct comparison unnecessary. Almost all the patients were in the low physical activity group [Table/Fig-2].

| Characteristics | Categories | Cachectic group | | Non cachectic group | | Precachectic group | |
|--|--------------|-----------------|------------|---------------------|------------|--------------------|------------|
| | | n (%) | Mean±SD | n (%) | Mean±SD | n (%) | Mean±SD |
| Age (years) | | 13 (100) | 49.46±5.22 | 11 (100) | 49.45±3.47 | 8 (100) | 48.13±6.22 |
| Gender | Male | 11 (84.6) | | 9 (81.8) | | 8 (100) | |
| | Female | 2 (15.4) | | 2 (18.2) | | 0 | |
| Height (in meters) | | | 1.68±0.05 | | 1.65±0.07 | | 1.68±0.03 |
| Weight before diagnosis (in kgs) | | | 62.38±7.33 | | 62.09±4.87 | | 61.5±6.93 |
| Weight after diagnosis (in kgs) | | | 55±5.74 | | 60.73±4.98 | | 59.13±7.20 |
| BMI before diagnosis (in kg/m ²) | | | 22±2.04 | | 23±2.93 | | 21.75±2.38 |
| BMI after diagnosis (in kg/m ²) | | | 19.62±1.89 | | 22.55±2.94 | | 21±2.45 |
| Location of cancer | Transglottis | 2 (15.4) | | 0 | | 0 | |
| | Tongue | 5 (38.5) | | 0 | | 0 | |
| | Nasopharynx | 1 (7.7) | | 0 | | 2 (25) | |
| | Buccal | 3 (23.1) | | 7 (63.6) | | 4 (50) | |
| | Oropharynx | 1 (7.7) | | 0 | | 1 (12.5) | |
| | Lip | 0 | | 1 (9.1) | | 1 (12.5) | |
| | Oral cavity | 1 (7.7) | | 3 (27.3) | | 0 | |
| Stage of Cancer (TNM) | I | 0 | | 0 | | 1 (12.5) | |
| | II | 2 (15.4) | | 5 (45.5) | | 3 (37.5) | |
| | III | 7 (53.8) | | 5 (45.5) | | 3 (37.5) | |
| | IV | 4 (30.8) | | 1 (9.1) | | 1 (12.5) | |
| ECOG | 0 | 2 (15.4) | | 2 (18.2) | | 1 (12.5) | |
| | 1 | 4 (30.8) | | 7 (63.6) | | 4 (50) | |
| | 2 | 3 (23.1) | | 2 (18.2) | | 2 (25) | |
| | 3 | 4 (30.8) | | 0 | | 1 (12.5) | |
| Weight loss % | | | 11.54±5.71 | | 2.18±0.75 | | 4.13±0.99 |
| CASC-IN Score | | | 12.69±5.94 | | 6.14±3.19 | | 14.06±2.92 |

[Table/Fig-1]: General characteristics of the participants.

| Variables | Categories | Cachectic group | Non cachectic group | Precachectic group |
|--------------------------------|------------|-----------------|---------------------|--------------------|
| | | n (%) | n (%) | n (%) |
| Physical activity (IPAQ score) | Low | 12 (92.3%) | 10 (90.9%) | 8 (100%) |
| | Moderate | 1 (7.7%) | 1 (9.1%) | 0 |

[Table/Fig-2]: Distribution of samples as per IPAQ categories.

Cachectic patient's demonstrated markedly reduced grip strength compared to both non cachectic and precachectic groups. Statistical analyses using ANOVA confirmed significant differences ($F=13.619$, $p\text{-value}<0.001$), post-hoc analysis showed cachectic vs non cachectic ($p\text{-value}<0.001$) and non cachectic vs precachectic ($p\text{-value}=0.032$), and a large effect size ($\eta^2=0.48$), indicating strong discriminatory power. Overall, HGS emerged as a robust marker of muscle function and cachexia severity, clearly distinguishing between groups [Table/Fig-3,4].

Walking distances were comparable across all groups, and statistical analysis confirmed no significant differences ($F=1.558$, $p\text{-value}=0.228$). This may imply that gross ambulatory function is largely preserved across cachexia stages. 6MWD may not be a discriminatory marker for detecting early functional decline in this population [Table/Fig-3,4].

| Variables (Outcome) | Cachectic group | Non cachectic group | Precachectic group | f-value | p-value | Effect size |
|-------------------------------------|-----------------|---------------------|--------------------|---------|---------|-------------|
| | Mean±SD | Mean±SD | Mean±SD | | | |
| Weight loss % | 11.54±5.71 | 2.18±0.75 | 4.13±0.99 | 20.838 | <0.001 | 0.59 |
| Hand grip strength (Dominant) (lbs) | 28.43±2.86 | 40.43±7.81 | 33.3±5.43 | 13.619 | <0.001 | 0.48 |
| Functional capacity (6MWD) (m) | 393.92±16.45 | 404.18±18.09 | 392.25±15.03 | 1.558 | 0.228 | |
| Physical activity (IPAQ in METS) | 224.31±170.02 | 344.55±232.05 | 115.62±59.36 | 3.937 | 0.031 | 0.21 |
| Quality of life (QoL) (FAACT score) | 53.61±14.79 | 70.33±11.12 | 51.69±7.71 | 7.519 | 0.002 | 0.34 |

[Table/Fig-3]: Intergroup Comparison of assessed parameters.

Physical activity levels differed significantly across groups ($p\text{-value}=0.031$), with non cachectic patients showing the highest METs and precachectic patients the lowest. Post-hoc analysis confirmed a difference between non cachectic and precachectic patients ($p\text{-value}=0.028$). Nearly all participants were classified as having low activity [Table/Fig-3], and the moderate effect size ($\eta^2=0.21$) indicates meaningful differences across group. These findings suggest that functional decline may begin early, even before substantial weight loss, and the moderate effect size indicates meaningful differences across groups [Table/Fig-3,4].

QoL differed significantly across groups ($p\text{-value}=0.002$), with non cachectic patients reporting the highest scores. Post-hoc analysis showed cachectic vs non cachectic ($p\text{-value}=0.007$) and non cachectic vs precachectic ($p\text{-value}=0.008$), and a moderate effect size ($\eta^2=0.34$), both cachectic and precachectic patients had substantially lower QoL. Again, the precachectic group reported the lowest scores. This suggests that subjective wellbeing may deteriorate early, even before full cachexia develops [Table/Fig-3,4].

DISCUSSION

The findings of this study showed notable physical activity and QoL reduction in the precachexia stage indicating the presence of early,

| Variable | Group | p-value | Level of significance |
|----------|----------|---------|-----------------------|
| HGS-D | CC vs NC | <0.001 | Significant |
| | CC vs PC | 0.192 | Non Significant |
| | NC vs PC | 0.032 | Significant |
| 6MWD | CC vs NC | 0.435 | Non significant |
| | CC vs PC | 1 | Non significant |
| | NC vs PC | 0.406 | Non significant |
| IPAQ | CC vs NC | 0.325 | Non significant |
| | CC vs PC | 0.548 | Non significant |
| | NC vs PC | 0.028 | Significant |
| FAACT | CC vs NC | 0.007 | Significant |
| | CC vs PC | 1 | Non significant |
| | NC vs PC | 0.008 | Significant |

[Table/Fig-4]: Post-hoc analysis using Bonferroni test.

CC: Cachexia; NC: Non-cachexia; PC: Pre-cachexia

multidimensional impairment before measurable weight loss. Also, HGS emerged as a discriminative measure of functional decline across cachexia stages.

In the present cohort, precachectic patients demonstrated higher CASC-IN scores along with reduced HGS, lowest physical activity, and poorer FAACT scores. This supports the concept that precachexia is an early, symptom-driven stage characterised by declining functional capacity and QoL despite limited weight loss. This aligns with the definition of precachexia, which emphasises early features such as reduced appetite and functional decline in the absence of significant weight loss [1]. Together, these findings suggest that impairments in muscle function and daily activity may emerge early in the disease trajectory, potentially preceding obvious metabolic deterioration. It also highlights CASC-IN as a sensitive tool capable of capturing these early clinically important and subtle changes in the precachexia stage.

Among the present cohort, precachectic patients exhibited markedly reduced physical activity levels. In earlier stages of cachexia, symptoms and psychosocial factors such as fatigue, pain, anxiety, and distress may negatively influence patient's functioning and activity levels before severe wasting becomes evident [24]. A previous study has similarly reported lower physical activity in precachectic and cachectic patients compared to non cachectic individuals. However, these differences did not always reach statistical significance, indicating that there may be a potential trend toward early [25]. This is supported by evidence from lung cancer populations, where lower IPAQ-SF scores were significantly associated with a higher risk of developing cachexia and remained an independent predictor after adjusting for confounders [15]. Objective data from a previous study using accelerometer-based measurements have also demonstrated reduced physical activity in cachectic head and neck cancer patients [26]. Unlike wearable accelerometers, the IPAQ-SF offers a simple, quick, and globally standardised method that is feasible for use in outpatient clinical settings [15].

Grip strength is a general indicator of muscle strength as it is associated with upper body strength [27]. As it has been strongly associated with morbidity, mortality, nutrition, and chronic disease, it is considered a new "vital sign" of health across the lifespan [28]. HGS is also found to be the most frequently measured physical function assessment in both cross-sectional and interventional studies [12]. In the present cohort, HGS clearly differentiated between cachexia stages, with cachectic patients showing the most pronounced deficits. Even non cachectic patients demonstrated values well below normative Indian data, underscoring that muscle weakness is an established feature of head and neck cancer irrespective of cachexia status [29]. These findings align with systematic review reporting reduced HGS as the most consistent marker of cachexia, typically accompanied by lower performance status scores [12].

As per recent systematic review on end-points in cachexia trials, FAACT emerged as the only cachexia-specific QoL instrument used across the reviewed trials [30]. In this cohort, FAACT scores were lower across precachexia and cachexia groups compared to non cachectic patients, reflecting substantial impairment in perceived wellbeing. These values are notably lower than those reported by a previous study, which observed a mean FAACT score of 93.2 in patients with advanced NSCLC cachexia. The lower scores maybe attributed to disease severity, patient characteristics, and study populations [16]. This range demonstrates the instrument's ability to capture the wide spectrum of health-related QoL experiences among cancer patients with cachexia [16]. FAACT scores may be lower in precachectic patients because anorexia (FAACT ≤ 30) forms part of the precachexia definition used in previous studies, suggesting that appetite-related QoL impairment may already be present in the early stages of cachexia [31,32]. A previous study reported significantly reduced FAACT scores in cachexia patients with end-stage kidney disease compared with non cachectic peers, further supporting its sensitivity [33].

In present study, 6MWD was similar across cachexia groups, indicating that this measure may lack discriminatory ability to detect early functional decline. Compared with normative values reported in healthy Indian adults, all groups demonstrated reduced performance, underscoring that functional capacity is compromised in head and neck cancer irrespective of cachexia status [34]. Prior studies have reported comparable reductions, with baseline values around 475 m in cachectic patients [35], and approximately 408 m in broader head and neck cancer cohorts [36]. The absence of significant differences across cachexia stages may reflect pacing strategies, ceiling effects, or the limited sensitivity of 6MWD in cross-sectional designs. Consistent with systematic reviews, 6MWD was less effective for distinguishing cachexia stages, likely because overall endurance remains relatively preserved in the early phases of cachexia. However, it remains a useful measure for tracking longitudinal changes and evaluating the impact of interventions over time [12].

This study provides novel insights into functional decline across cachexia stages in head and neck cancer patients at diagnosis or while awaiting treatment. A key strength is the use of simple, inexpensive, and clinically feasible tools such as CASC-IN, IPAQ-SF, and FAACT, which together offered a multidimensional perspective by capturing both objective function and patient-reported wellbeing without reliance on advanced imaging. The present study findings also suggest that patients identified as precachectic may benefit from early supportive interventions, such as quality-of-life programs, nutritional counselling, and physical activity support. Future trials should prioritise this subgroup as a critical window for early intervention and validate these findings with longitudinal study design.

Limitation(s)

The study had a small sample size, which limited statistical power. Recruitment challenges were mainly due to patient non cooperation at diagnosis, perceived burden of disease, and resource constraints. Physical activity was assessed using the IPAQ-SF, which captures values at a single time point. Body-worn accelerometers requiring longitudinal monitoring were not feasible with the study design. QoL was assessed using the FAACT questionnaire, which is subject to recall and reporting bias, although patient-reported outcomes remain valuable for capturing perceived wellbeing. Inflammatory status was assessed only using CRP alone, which may not fully represent the complexity of systemic inflammation. However, CRP is a practical and cost-effective biomarker and was used in accordance with CASC-IN criteria to support staging in precachexia. These methodological constraints should be considered when interpreting the findings.

CONCLUSION(S)

This cross-sectional study demonstrated stage-specific differences in HGS, physical activity, and QoL among head and neck cancer patients across the cachexia spectrum. Non cachectic patients maintained better muscle strength, physical activity, and QoL, whereas precachectic patients already showed moderate weight loss, reduced grip strength, and markedly lower activity and wellbeing. Cachectic patients experienced the greatest weight loss and lowest muscle strength, but their QoL was comparable to precachexia, reflecting the multidimensional burden of the syndrome. Functional decline begins early, with HGS and physical activity emerging as sensitive markers. Targeting patients in the precachexia stage may offer a critical window for timely intervention to prevent further functional deterioration.

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PARTICULARS OF CONTRIBUTORS:

1. PhD Scholar, Department of Physiotherapy, Dr. D. Y. Patil University, School of Physiotherapy, Nerul, Navi Mumbai, Maharashtra, India.
2. Professor and Head, Department of Musculoskeletal Physiotherapy, Dr. D. Y. Patil University, School of Physiotherapy, Nerul, Navi Mumbai, Maharashtra, India.
3. Professor and Head, Department of Ear, Nose, and Throat, Dr. D. Y. Patil University, School of Medicine, Nerul, Navi Mumbai, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Bindya Sharma,
S4-103, Godrej Prime, Tilak Nagar East, Mumbai-400071, Maharashtra, India.
E-mail: drbindya.sharma@gmail.com

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