**Original Article**

# Quality of life and Indian Diabetes Risk Score are linked to heart rate variability in young individuals with prediabetes and diabetes in India

**Gorantla Shravya Keerthi, Pravati Pal, Gopal Krushna Pal, Jaya Prakash Sahoo[1], Magadi Gopalakrishna Sridhar[2], Jayaraman Balachander[3]**

*Departments of Physiology, [1]Endocrinology, [2]Biochemistry, and [3]Cardiology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India*

## Abstract

**Background and Aim:** Although diabetes is known to be associated with cardiac autonomic neuropathy and depressed quality of life (QoL) in terms of physical and psychological domains due to the disease duration and complications, till date no reports are available to show the link between QoL and Indian Diabetes Risk Score (IDRS) with cardiac autonomic neuropathy assessed with heart rate variability (HRV) in newly diagnosed type 2 diabetes mellitus and prediabetes without comorbidities. IDRS is known to predict cardiometabolic risks, neuropathy and future diabetes risk even in normoglycemic subjects. Hence, in this study, we have planned to assess the plausible link between QoL scale and IDRS with HRV in young Indian individuals with newly diagnosed diabetes and prediabetes.

**Methods:** Among 328 (18–45 years) age-matched individuals, 78 were included as controls, 126 in prediabetes group, and 124 in newly diagnosed diabetes group. Subject's QoL and IDRS were assessed by questionnaires, and resting HRV were recorded. Fasting blood glucose (FBG) and fasting insulin was estimated, and homeostatic model assessment of insulin resistance (HOMA-IR) was calculated. Independent association of ratio of low-frequency to high-frequency power (LF: HF ratio) with other variables was analyzed by multiple regression analysis.

**Results:** HRV and QoL were significantly decreased; IDRS, FBG, fasting insulin, and HOMA-IR were significantly increased in prediabetes and diabetes group compared to controls with an equal level of significance. Furthermore, these parameters showed significant difference that was more intense in diabetes group compared with prediabetes group.

**Conclusion:** The association of sympathovagal imbalance in terms of LF: HF ratio with QoL and IDRS was found in Indian adults with prediabetes and diabetes even in the younger age without having any disease complications.

**Key words:** Diabetes, heart rate variability, Indian Diabetes Risk Score, prediabetes, quality of life, sympathovagal imbalance

## INTRODUCTION

The quality of life (QoL) is defined as the overall impact of the therapeutic condition on the physical and societal functioning, and psychological well-being, and also regarded as "the ultimate goal of all health interventions."[1] The QoL scale, created originally by John Flanagan, American psychologist in the 1970's, has been adapted for use in chronic illness groups.[2] QoL measurement provides a significant way to determine

**Address for correspondence:** Dr. Pravati Pal, Department of Physiology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry - 605 006, India.
E-mail: drpravatipal@gmail.com

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the impact of health management on individuals suffering from chronic diseases when cure is not possible. It is frequently used as an outcome measurement and yields complementary information to epidemiological or medical data.[1] The QoL scale has been used in studies of healthy adults and patients with diabetes mellitus, heart disease, fibromyalgia, rheumatic diseases, COPDs, gastrointestinal disorders, spinal cord injury, psoriasis, and stress-related disorders. Flanagan QoL scale was used in this study as it is a simple questionnaire compared to other health-related QoL questionnaires and its reliability and validity have been tested in diabetes.[2]

Type 2 diabetes mellitus (T2DM) is one of the chronic diseases and India occupies 19% of world's diabetic population.[3] In developed countries, T2DM mostly affects elderly; but in developing countries like India, the working lives of the younger population are affected causing a threat to their health.[4] Diabetic people often feel challenged by their disease, day-to-day management, and its substantial demands. Cardiovascular autonomic neuropathy (CAN) is one of the most unnoticed of all major complications of T2DM and is associated with poor prognosis and decline in QoL affecting individual's daily activities.[5] CAN encompasses when sympathetic and vagal fibers of the cardiovascular (CV) system are involved leading to disturbances in neurohormonal regulation affecting heart rate and vascular dynamics. Clinically, sympathovagal modulation on sinus node automaticity is assessed by a non-invasive sensitive tool, the spectral analysis of heart rate variability (HRV) in various health and disease conditions.[6] CAN is more prevalent in T2DM patients (34%), appearing even before the diagnosis of diabetes, a stage called prediabetes and in metabolic syndrome due to prolonged dysglycemia.[7]

Prediabetes, often asymptomatic and undiagnosed, is almost fuelling the epidemics of T2DM and its consequences worldwide.[8] In 2013, the American Diabetes Association (ADA) defined prediabetes as impaired fasting glucose (IFG) of 100–125 mg/dl or impaired glucose tolerance of 140–199 mg/dl, 2 h values in oral glucose tolerance test (OGTT).[9] Global estimation predicts that by 2030 more than 470 million and 439 million adults will have prediabetes and T2DM, respectively.[10] Greater than 50% of population with T2DM remain undiagnosed, and the majority of them with CAN remain asymptomatic for decades.[11] Indian Diabetes Risk Score (IDRS) developed by Madras Diabetes Research Foundation (MDRF) based on individual's age, gender, family history of diabetes, waist circumference (WC), and physical activity is cost-effective than performing OGTT to screen undiagnosed T2DM in India.[12] IDRS is a simplified diabetes risk score compared to other diabetes risk scores as it uses four simple easily obtainable risk factors recommended from ADA. In a large metropolitan

city of India, the demography of which is similar to the rest of the India with diversified food habits and cultures, the study was conducted on a very high-risk population and the IDRS was developed. IDRS did not include questions on a diet as it was difficult to standardize the portion of food across different socioeconomic groups. IDRS helps to recognize metabolic syndrome and cardiometabolic risks in subjects with normoglycemia and arterial stiffness in nondiabetic individuals and is also associated with complications of diabetes such as neuropathy and peripheral vascular disease.[13] Hence, we included MDRF - IDRS in this study, due to its simplicity and advantages over other diabetes risk scores and also useful to identify the risk of developing diabetes or prediabetes in future in spite of normoglycemic levels.

In diabetes, it is reported that reduced HRV is associated with duration of disease, hyperinsulinemia, obesity, hypertension, and retinopathy; and is an independent risk factor for CV morbidity and mortality.[5] Although many studies have reported the association of T2DM with deteriorated QoL and CAN in elderly or with disease complications and mostly in western population,[14] to our knowledge, there are no reports available assessing the link between QoL scale and diabetes risk score with HRV in young adult individuals with prediabetes and newly diagnosed diabetes without complications. Therefore, in the present work, we aimed to study the association between sympathovagal imbalance (SVI) in terms of Ratio of low-frequency to high-frequency power (LF:HF ratio) with QoL and IDRS in young Indian adults with prediabetes and diabetes.

## MATERIALS AND METHODS

### Study setting and participants

After getting the approval of Institute's scientific advisory and Ethics Committee, this study was conducted as a part of PhD thesis work in the CV research laboratory, department of Physiology, JIPMER, Puducherry, India. Based on ADA 2013 criteria,[9] normotensive participants (systolic blood pressure: 100–119 mm of Hg; diastolic blood pressure: 60–79 mm of Hg) in the age group of 18–45 years were screened for prediabetes, and newly diagnosed diabetes (Fasting blood glucose [FBG] ≥126 mg/dl) patients were recruited from Endocrinology outpatient clinic of JIPMER. Age- and gender-matched healthy volunteers were recruited as controls. Before the initiation of the study, written informed consent was obtained from all the subjects. Subjects with any chronic illness, prehypertension, hypertension, CVD, medication influencing glycemic levels and other endocrine disorders were excluded from the study. Among 328 participants, 78 were included in control group, 126 in prediabetes group and 124 in diabetes group in this study.

## Brief procedure

The procedures were performed in a silent ambient room with minimal lighting at 24–26°C of room temperature. Participants reported at 8 AM to the laboratory after overnight fasting, and 5 ml of venous blood was collected under aseptic precautions for the estimation of FBG and insulin. The FBG was estimated by GOD-POD method (Genuine Biosystem, Chennai, India) and Insulin by ELISA kit (BIORAD Evolis system, Marnes-La-Coquette, France). Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using the formula: Fasting insulin ($\mu$IU/mL) × fasting glucose (mg/dl)/405.[15]

Participant's personal history such as smoking, alcoholism, occupation, and physical activity, family history of diabetes, and relevant medical history was taken. WC in cm and hip circumference in cm of the participants were measured, and waist–hip ratio (WHR) was calculated. MDRF - IDRS questionnaire was used to calculate diabetes risk score that is based on age, gender, family history of diabetes, WC, and physical activity.[12] QoL of the subjects was assessed using Flanagan QoL scale, a 16 item questionnaire that includes material and physical well-being, peer relationships, social well-being, personal development and fulfillment, recreation and independence.[2] The instrument is scored by adding up the items to make a total score. Scores can range from 16 to 112. An average total score of healthy individuals is about 90. They were encouraged to fill out every item even if they are not currently occupied in it. The mean score was entered for the item for missing data.

## Short-term heart rate variability recording and analysis

After 15 min of supine rest, electrocardiogram (ECG) was recorded for 5 min for short-term HRV following the standard procedure as per the guidelines of Task Force for HRV.[16] Using 16-bit, 16-channel BIOPAC MP 150 data acquisition system (BIOPAC Inc., Goleta, CA, USA) the lead II ECG was acquired at a rate of 1000 samples per second. The recorded resting lead II ECG using band pass filter (2 Hz to 40 Hz) was carefully analyzed for artifacts and ectopic beats, which were removed thoroughly. The data from BIOPAC to a windows-based PC were transferred using acknowledge software version 4.2. Both time domain and frequency domain measures were analyzed using HRV analysis software (Version 2.0., Biomedical Signal Analysis group, University of Kupio, Finland) and fast Fourier transform algorithm. Frequency domain analysis components were depicted as spectral power such as total power (TP), normalized LF power (LFnu), normalized HF power (HFnu), LF-HF ratio, and time-domain components which encompassed square root of the mean squared differences of successive normal to normal intervals (RMSSD) and standard deviation of normal to normal (SDNN) interval were calculated.

## Statistical analysis

SPSS 16.0 (SPSS Inc., Chicago, IL, USA) for Windows was used to analyze the data after checking for normal distribution. The data were represented as mean ± standard deviation and median (interquartile range). The intergroup comparison was performed using one-way ANOVA and *post hoc* analysis was done by Tukey for normal data and Kruskal–Wallis test for non-parametric data. The correlation of LF:HF ratio with QoL, IDRS, and glucose-related parameters was assessed by Spearman rank correlation. The independent contribution of these parameters to LF:HF ratio was assessed by multiple regression analysis. Calculations were based on two-sided 95% confidence interval and 80% power, and $P < 0.05$ was considered statistically significant.

## RESULTS

Age showed no significant difference among three groups [Table 1]. WHR showed a significant difference in prediabetes and diabetes group compared to controls, but there was no significant difference found between prediabetes and diabetes groups. In the short-term HRV parameters, LFnu and LF:HF ratio were significantly increased ($P < 0.001$) and TP, HFnu, RMSSD, and SDNN were decreased significantly in prediabetes and diabetes groups compared to controls. TP and RMSSD were reduced significantly ($P < 0.001$) in subjects with diabetes compared to prediabetes.

Table 2 shows a significant increase ($P < 0.001$) in FBG, insulin, HOMA-IR, IDRS; and a significant decrease in QoL scale ($P < 0.001$) in prediabetes and diabetes group compared to controls. Moreover, these parameters showed significant difference between prediabetes and diabetes subjects.

The Spearman correlation showed significant positive relation between LF:HF ratio with FBG, insulin, HOMA-IR, and IDRS; and significant negative correlation with QoL scale [Table 3]. Table 4 shows multiple regression analysis that assessed the independent association of LF:HF ratio (dependent variable) with FBG, insulin, HOMA-IR, IDRS, and QoL scale (independent variables) in study groups. In this study, there was significant independent contribution of FBG, insulin, HOMA-IR, IDRS, and QoL scale to LF:HF ratio in subjects with prediabetes and diabetes.

## DISCUSSION

Although diabetes mellitus is known to cause CV autonomic dysfunction since a long time and lead to decreased QoL and well-being in these patients, a

**Table 1:** Comparison of parameters between controls, prediabetes, and diabetes

| Parameter | Controls (*n*=78) | Prediabetes (*n*=126) | Diabetes (*n*=124) |
|---|---|---|---|
| General characteristics and anthropometric parameters | | | |
|   Age (years) | 36.80±6.05 | 35.96±6.37 | 37.33±6.25 |
|   Waist-hip ratio | 0.91±0.05 | 0.94±0.05* | 0.96±0.07*** |
| HRV parameters | | | |
|   TP (ms²) | 1170.00 (815.00-1615.50) | 755.50 (507.00-1328.00)** | 495.00 (288.00-701.00)***,### |
|   LFnu | 40.20 (33.15-46.22) | 64.70 (57.10-73.40)*** | 64.40 (55.62-77.20)*** |
|   HFnu | 59.80 (53.77-66.85) | 35.30 (26.60-42.90)*** | 35.00 (22.75-44.15)*** |
|   LF:HF ratio | 0.67 (0.49-0.83) | 1.83 (1.32-2.75)*** | 1.84 (1.25-3.39)*** |
|   RMSSD (ms) | 32.95 (22.40-53.70) | 23.10 (16.55-28.92)*** | 19.10 (14.50-25.77)***,### |
|   SDNN (ms) | 39.10 (29.20-53.57) | 29.75 (20.27-39.45)* | 26.80 (19.85-30.97)** |

Data are expressed as mean±SD or median (IQR). *Comparison of controls versus prediabetes and diabetes, #Prediabetes versus diabetes. *$P<0.05$, **$P<0.01$, ***$P<0.001$; #$P<0.05$, ##$P<0.01$, ###$P<0.001$. TP: Total power, LFnu: Normalized low-frequency power, HFnu: Normalized high-frequency power, LF: HF ratio: Ratio of low-frequency to high frequency power, RMSSD: The square root of the mean of the sum of the squares of the differences between adjacent NN intervals, SDNN: Standard deviation of normal to normal interval, HRV: Heart rate variability, SD: Standard deviation, IQR: Interquartile range

**Table 2:** Comparison of glucose related parameters, Indian Diabetes Risk Score and quality of life between controls, prediabetes, and diabetes

| Parameter | Controls (*n*=78) | Prediabetes (*n*=126) | Diabetes (*n*=124) |
|---|---|---|---|
| FBG (mg/dl) | 83.01±9.70 | 114.57±5.63*** | 165.79±16.33***,### |
| Fasting insulin (µIU/ml) | 5.88±2.26 | 21.31±6.73*** | 33.25±9.43***,### |
| HOMA-IR | 1.20±0.49 | 6.08±2.01*** | 13.88±5.35***,### |
| QoL scale | 89.70±5.85 | 65.70±15.11*** | 57.91±16.55***,### |
| IDRS | 44.11±9.31 | 72.69±12.02*** | 76.12±9.34***,# |

Data are expressed as mean±SD; *Comparison of controls versus prediabetes and diabetes, #Prediabetes versus diabetes. *$P<0.05$, **$P<0.01$, ***$P<0.001$; #$P<0.05$, ##$P<0.01$, ###$P<0.001$. HOMA-IR: Homeostatic model assessment of insulin resistance, FBG: Fasting blood glucose, QoL scale: Quality of life scale, IDRS: Indian Diabetes Risk Score

**Table 3:** Spearman correlation of low-frequency:high-frequency power ratio with glucose related parameters, Indian Diabetes Risk Score and quality of life between controls, prediabetes, and diabetes

| Parameter | Controls (*n*=78) | | Prediabetes (*n*=126) | | Diabetes (*n*=124) | |
|---|---|---|---|---|---|---|
| | *r* | *P* | *r* | *P* | *r* | *P* |
| FBG | 0.175 | 0.124 | 0.302 | 0.001 | 0.307 | 0.001 |
| Fasting insulin | 0.092 | 0.425 | 0.250 | 0.005 | 0.488 | 0.000 |
| HOMA-IR | 0.055 | 0.635 | 0.290 | 0.001 | 0.526 | 0.000 |
| QoL scale | −0.169 | 0.139 | −0.650 | 0.000 | −0.654 | 0.000 |
| IDRS | 0.034 | 0.765 | 0.430 | 0.000 | 0.417 | 0.000 |

FBG: Fasting blood glucose, HOMA-IR: Homeostatic model assessment of insulin resistance, QoL scale: Quality of life scale, IDRS: Indian Diabetes Risk Score

**Table 4:** Multiple regression analysis of low-frequency:high-frequency power ratio (dependent variable) with various independent variables in prediabetes and diabetes

| Parameter | Prediabetes (*n*=126) | | | Diabetes (*n*=124) | | |
|---|---|---|---|---|---|---|
| | β | 95% CI | *P* | β | 95% CI | *P* |
| FBG | 0.320 | 0.029-0.092 | 0.000 | 0.307 | 0.015-0.053 | 0.001 |
| Fasting insulin | 0.256 | 0.015-0.074 | 0.004 | 0.488 | 0.076-0.148 | 0.000 |
| HOMA-IR | 0.310 | 0.082-0.277 | 0.000 | 0.526 | 0.169-0.308 | 0.000 |
| QoL scale | −0.677 | −0.062-−0.042 | 0.000 | −0.654 | −0.116-−0.076 | 0.000 |
| IDRS | 0.461 | 0.029-0.060 | 0.000 | 0.417 | 0.066-0.151 | 0.000 |

FBG: Fasting blood glucose, HOMA-IR: Homeostatic model assessment of insulin resistance, QoL scale: Quality of life scale; IDRS: Indian Diabetes Risk Score, CI: Confidence interval

recent study report has shown declined QoL score in prediabetes population with high body mass index and decreased physical activity.[14,17] These studies included population with mean age greater than 50 ± 8.3 years and in western countries.[14,17,18] Prediabetes subjects are at high risk of developing T2DM within 5–10 years and CV diseases.[8] In developing countries like India, T2DM depends on urbanization, lifestyle changes and family

history of diabetes, increasing the risk of development of prediabetes and diabetes, mostly affecting the younger people. However, there is no study in Indian subcontinent reporting the association of QoL with autonomic function in young adult population with prediabetes and diabetes. Therefore, in this study, we have planned to assess the link of depressed QoL with SVI through HRV (LF:HF ratio). Furthermore, we have attempted to assess the relation between SVI and IDRS that is developed for Asian Indians with unique risk factors.

This study revealed the comparison of glucose-related parameters, QoL scale, and IDRS and their association with SVI in prediabetes and diabetes individuals of 28–40 years of age. This younger age group which is actively involved in work suffer from psychosocial work stress that leads to reduced work productivity and job satisfaction affecting economic status.[19] This kind of work stress was reported to be associated with decreased HRV and CV morbidity.[20] The HRV parameters, TP, HFnu, RMSSD, and SDNN representing cardiac vagal modulation[16] were attenuated and LFnu indicating sympathetic activity and LF:HF ratio representing SVI were increased significantly in prediabetes and diabetes subjects with almost equal magnitude compared to controls [Table 1]. The SVI in prediabetes and diabetes was due to alteration in both sympathetic and vagal activities. Thus, vagal tone might decline with autonomic dysfunction shifting towards heightened sympathetic activity during the progression from normoglycemia to prediabetes and to diabetes. Autonomic nervous system (ANS) has an effect on different organ systems through its sympathetic and vagal branches involved in energy mobilization, and vegetative and restorative functions, respectively.[21] A balanced dynamic relationship between two ANS branches is necessary for normal bodily functions and to maintain day-to-day activities of the individual. Increased LF:HF ratio in prediabetes and diabetes indicated imbalance between these two systems with sympathetic hyperactivity and vagal withdrawal. Excessive sympathetic activation for long time in these individuals might not withstand the energy demands of the body systems finally affecting their physical functions, thereby declining the QoL. Even though the FBG is in borderline range in prediabetes, and the diabetes individuals were newly diagnosed without any other disease complications, the SVI could be affecting the daily activities and well-being of the individual indicated by decreased QoL scale as it had shown negative relation with LF:HF ratio with multiple regression analysis. IDRS was known to be associated with neuropathy even after adjusting for duration of diabetes, but the relationship between HRV and IDRS was not established.[13] We found significant association between LF:HF ratio and IDRS indicating that there was increased risk of developing diabetes complications due to SVI and also it had a negative impact on the QoL of the individuals.

The glucose-related parameters such as FBG, insulin, and HOMA-IR were significantly increased in study groups compared to controls, and the rise was more significant in diabetes compared to prediabetes [Table 2]. Insulin sensitivity was inversely related to glycemic status; even within the normal fasting glucose range, the increase in FBG levels from 70 to 125 mg/dl was associated with a >3-fold decrease in insulin sensitivity.[22] Individuals with isolated IFG showed approximately 25% increase in IR compared with individuals with normal FBG levels.[22] QoL scale was declined and IDRS increased significantly in prediabetes and diabetes compared to controls [Table 2]. Individuals with diabetes showed marked decline in QoL scale compared to prediabetes. IDRS value of <30 is considered as low risk, between 30 and 50 as medium risk, and ≥60 as high risk for diabetes. Furthermore, it is helpful to determine insulin resistance syndrome and cardiometabolic risks in subjects with normal glucose levels.[13] This study observed IDRS ≥70 in prediabetes and diabetes group, showing increased risk of diabetes in prediabetes individuals and the risk score was equally significant in both groups [Table 2]. IDRS ≥60 determines the prevalence of hypertension, hypertriglyceridemia, hypercholesterolemia, neuropathy, and metabolic syndrome.[13]

In this study, levels of glucose-related parameters, QoL scale, and IDRS in study subjects were not only significantly high but also correlated significantly with LF:HF ratio of HRV [Table 3]. Furthermore, in multiple regression analysis, QoL scale, IDRS, FBG, insulin, HOMA-IR, showed the independent contribution to LF:HF ratio, a marker of SVI [Table 4]. Thus, it shows that depressed QoL, increased IDRS and insulin resistance are closely associated with LF:HF ratio representing cardiac autonomic dysfunction in prediabetes and diabetes individuals. Hence, SVI might be the possible pathophysiological link between glycemic status, QoL and well-being in prediabetes individuals and newly diagnosed diabetes patients. The insulin receptors are expressed in brain areas such as prefrontal cortex, amygdala, raphe nucleus, hippocampus, hypothalamus and striatum, and these areas are involved in pathogenesis of disorders in mood and behavior.[23] The plausible explanation for decreased QoL, depression, and well-being might be due to disruption of insulin signaling in these areas leading to impairment in dopaminergic and serotonin neuronal pathways involved in depression and known to contribute to mood disorders in diabetes.[24] Chronic hyperinsulinemia by exerting a direct effect on hypothalamus lead to sympathetic hyperactivity and vagal withdrawal and impairs sinoatrial node sensitivity to sympathovagal influences and modulation that lead to alterations in HRV.[25]

Previous studies have reported that QoL and cardiac autonomic neuropathy is linked to the old age, duration of diabetes and with comorbidities. However, we found increased IDRS, declined HRV, and QoL scale in newly diagnosed diabetes subjects without complications and prediabetes individuals in younger age, which is the novelty of our study. Therefore, early identification of SVI with diabetes risk scoring and lifestyle modifications might be helpful to prevent progression from initial stages to irreversible stages of the disease and also to improve glycemic management, social, mental, and physical functioning of the individuals. It is reported from our laboratory that sympathovagal homeostasis is restored; QoL and metabolic function is improved by techniques of yoga and relaxation attenuating the CV risks.[26-28]

### Limitations of the study

Subjects were screened and diagnosed based on their consecutive FBG levels but not by OGTT. Hence, IDRS which is validated with diabetes risk factors without performing OGTT was used in the study.

## CONCLUSION

In this study, we addressed the mechanism of SVI affecting the QoL in prediabetes and diabetes subjects even in the younger age. To our knowledge, this is the first Indian study reporting the link between HRV with QoL and IDRS in young adults with newly diagnosed diabetes and prediabetes. Moreover, our study findings implicate that the level of contribution of glucose-related parameters, IDRS and QoL to SVI is important than the magnitude of these factors. Individuals with prediabetes are equally vulnerable as the diabetes patients. The reason might be that before they are diagnosed with T2DM, they spend many years in the stage of prediabetes without being screened. Although the HRV parameters are comparable between prediabetes and diabetes; the association of QoL and IDRS with cardiac autonomic imbalance is mildly intense in prediabetes than diabetes.

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### Conflicts of interest
There are no conflicts of interest.

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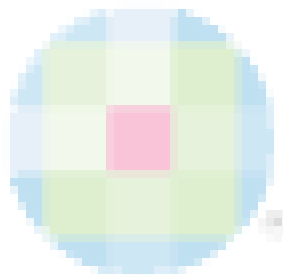
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  Sheahan P, O'leary G, Lee G, Fitzgibbon J. Cystic cervical metastases: Incidence and diagnosis using fine needle aspiration biopsy. Otolaryngol Head Neck Surg 2002;127:294-8.
- Only the references from journals indexed in PubMed will be checked.
- Enter each reference in new line, without a serial number.
- Add up to a maximum of 15 references at a time.
- If the reference is correct for its bibliographic elements and punctuations, it will be shown as CORRECT and a link to the correct article in PubMed will be given.
- If any of the bibliographic elements are missing, incorrect or extra (such as issue number), it will be shown as INCORRECT and link to possible articles in PubMed will be given.