

The obesity paradox - Is BMI associated with advanced stage in oral cancer?

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ABSTRACT

Background: Recent studies have shown that cancer patients with low BMI have poor outcomes. Their results suggest, obesity have some protective effect in cancer termed as “obesity paradox”.

Aim: To examine the association of BMI with prognostic indicators of oral squamous cell carcinoma (OSCC).

Methodology: This multicenter cross-sectional study was conducted during the year 2020 and 2021. 126 patients recently diagnosed with OSCC were randomly selected from three different tertiary care setup in Karachi. Height and weight of each subject was recorded to calculate BMI and clinicopathological data was obtained. The BMI indices were categorized into low, normal and high strata according to WHO guidelines. Statistical analysis was done for association of independent factors with BMI strata.

Results: We found 81(64.3%) participants were underweight compared to 32(25.4%) normal-weight and 13(10.3%) overweight cases. A strong statistical association was observed between low BMI (83.1% underweight) and advanced tumor stage i.e., Stage IV ($P=0.001$) while among risk factors of OSCC, only smokeless tobacco showed significant association ($P=0.002$) with reduced BMI. This research brings attention to the importance of BMI in cancer and add to the growing literature in the field of oncology. Our findings about the impact of BMI on OSCC outcome will help in the intervention and development of prevention strategies for one of the most prevalent cancers in Pakistan. This present research will help to answer the complex question of “optimum” BMI in cancer and will help to improve the prognosis of OSCC.

Conclusion: Our findings suggested that low BMI could be an indicator of poor clinical outcomes in OSCC. We thus recommend monitoring of BMI in OSCC patients in order to optimize treatment strategies. However, we encourage further studies to examine other body composition metrics for individualized treatments and intervention strategies.

Keywords: Adiposity, Obesity paradox, Squamous cells, carcinoma, BMI

INTRODUCTION

OSCC is an aggressive epithelial tumor of the head and neck region. It has a high prevalence rate that accounts for 377,713 new cases and 177,757 deaths in the year 2020¹. The major portion of this global burden is concentrated in South Central Asia, where the sub-continent represents the hardest hit region^{1,2}. The growing rate of OSCC in South Asia is mainly contributed by the consumption of tobacco products which have gained much popularity in recent years especially among younger population³. Besides tobacco, there are many confounders such as; physical inactivity, unhealthy diet, metabolic, environmental, social, economic, and psychological factors; all of which might have a suspected role in the OSCC morbidity and mortality.⁴ Most of these confounders contribute directly to buildup of body fat eventually leading to obesity, which is usually characterized by body Mass Index (BMI)⁵.

BMI is a mathematical interval, it's normal value ranges from 18.5–24.9kg/m². Value below 18.5kg/m² is categorized as underweight while estimates above 25kg/m² corresponds to an overweight individual. However, values over 30kg/m² is referred as obesity⁶. There is substantial evidence in the literature, which supports a strong relationship of obesity with increased risk for cancers and poor clinical outcomes⁷. Despite that, there are conflicting reports in the literature that favors better survival of patients which indicates that low BMI could be a better determinant of poor prognosis in many cancers⁸. This has led to the generation of a new hypothesis known as “obesity paradox”. “Obesity paradox” refer to the protective effect of obesity in cancer related mortality. In support of this hypothesis, increased survival had been reported by many authors in obese cancer patients⁹.

As the relationship of obesity is supported by numerous studies⁸, this new hypothesis triggers a debate for accurate BMI interval indicative of poor prognosis. In oral cancer, efforts to identify the influence of BMI on prognostic variable like tumor histology and TNM stage have yielded mixed results¹⁰. In this

context, most authors suggested that adiposity is strongly related to metabolic dysfunction which promotes tumor cell proliferation⁷. Whereas, few recent studies supports the theory of “obesity paradox”⁹. Given the controversial association of BMI with adverse outcomes, we explore the impact of BMI on prognostic indicators of the oral squamous cell carcinoma. We also sought to analyze the association of various independent risk factors of OSCC with BMI. The findings of this research will assist in better understanding of the effect of confounders on proliferative characteristics of one of the most prevalent cancer in Pakistan.

METHODOLOG

Study design and setting: A multicenter cross-sectional study was conducted after obtaining ethical approval from ethic review committee, Ziauddin University (Reference # 3520321JAPAT). This study was conducted during the year 2021 and all participants were receiving care at three different centers which includes Dr. Ziauddin Hospital, The laboratory Karachi, and Pakistan Navy Station Shifa (PNS Shifa), Karachi, Pakistan.

Participants: Total of 126 subjects were selected after seeking written informed consent. The inclusion criteria of our cases were biopsy confirmed Oral squamous cell carcinoma (OSCC) irrespective of age and gender. However, patients with any secondary malignancy to oral cavity were excluded from this research. All patients included in our research were receiving care for OSCC at respective centers during May 2021 to December 2021. The subjects were approached by visiting OPD's and wards delivering patients care to acquire clinical and demographic data. The measurements of height and weight were recorded and the laboratory data in relation to histological findings was retrieved. All data was collected by principal investigator via interviews and the output was entered in a predefined research proforma.

Assessment of BMI: Body Mass Index (BMI) were calculated for each subject by using formula “ $BMI = \text{weight(kg)} / \text{height(m)}^2$ ” and estimates were categorized according to WHO classification as low (<18.5kg/m²), normal (18.5kg/m²-24.9kg/m²) and high (>25kg/m²)⁶.

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Statistical analysis: SPSS version 24.0 was used for all statistical calculations. Age and gender were presented in term of mean and frequencies. Data was assessed for normality and chi-square test was applied to determine the association of categorical variables with the BMI indices. The same was done for all independent variables. P-value less than 0.05 was considered as statistically significant at 95% confidence interval.

RESULTS

Out of 126 participants, 81(64.3%) were underweight compare to 32(25.4%) normal-weight and 13(10.3%) overweight cases. There was male predominance (73.8%) as compare to female (26.2%). Majority of subjects were over forty years upon diagnosis and the median age for all subject was recorded as 51 years.

The determinants of tumor prognosis for OSCC showed that most cases (42.1%) were diagnosed as stage IV however, it was surprising to note that the overwhelming number (57.1%) of cases

were presented as well differentiated on histological grade. While comparing the BMI estimates with prognostic indicators, we found that more than two third (83.1%) of the subjects with stage IV disease had a low BMI. This accounts for a strong statistical association (P <0.05) of low BMI with an advanced stage disease. No statistical difference of BMI with tumoral grade was observed (Table I).

Our clinical data showed smokeless tobacco was the most popular (35.7%) substance of abuse among our subjects. High proportion of these subjects (73.3%) had a low BMI on diagnosis of oral cancer contributing to significant statistical association (P<0.05). Among tumor sites, buccal mucosa was the commonest site (55.6%) of origin for the malignant lesion. This was followed by tongue (17.5%) and rest of the oral cavity. None of the other independent variables were statistically related to the BMI. Table II presents the outline known risk factors and their relationship with categories of BMI.

Table I. Distribution of prognostic variables among cases of OSCC and BMI statistical estimates.

Prognostic Indicators	n=126	Low BMI (n=81)	Normal-BMI (n=32)	High BMI (n=13)	P value
Stage					
Stage I	9(7.6%)	3(33.3%)	5(55.5%)	1(11.1%)	0.01
Stage II	22(17.5%)	8(36.3%)	11(50%)	3(13.6%)	
Stage III	42(33.3%)	26(61.9%)	9(21.4%)	7(16.6%)	
Stage IV	53(42.1%)	44(83.1%)	7(13.2%)	2(3.77%)	
Grades					
Well differentiated	72(57.1%)	44(61.1%)	19(26.4%)	9(12.5%)	.602
Moderately differentiated	43(34.1%)	28(65.1%)	12(27.9%)	1(9.1%)	
Poorly differentiated	11(8.7%)	9(81.8%)	1(9.1%)	1(9.1%)	

Table II. Clinicopathological characteristics of OSCC patients and BMI characterization with descriptive statistics

Clinicopathological characteristics	n=126	Low BMI (n=81)	Normal-BMI (n=32)	High BMI (n=13)	P value***
Gender					
Male	93(73.8%)	64(68.8%)	21(22.5%)	8(8.7%)	.196
Female	33(26.1%)	17(51.5%)	11(33.5%)	5(15.1%)	
Age groups					
<40	25(19.7%)	16(64%)	7(28%)	2(8%)	.884
≥40	101(80.3%)	65(64.3%)	25(24.7%)	11(11%)	
Sites					
Lip	8(6.3%)	3(37.5%)	3(37.5%)	2(25%)	.017
Tongue	22(17.5%)	16(72.7%)	4(18.1%)	2(9%)	
Palate	8(6.3%)	1(12.5%)	4(50%)	3(37.5%)	
Buccal mucosa	70(55.6%)	51(72.8%)	16(22.8)	3(4.3%)	
Floor of mouth	5(4.0%)	2(40%)	1(20%)	2(40%)	
Retromolar area	4(3.2%)	2(50%)	2(50%)	0(0%)	
Gingiva	9(7.1%)	6(66.6%)	2(22.2%)	1(11.1%)	
Habits					
Smokeless	45(35.7%)	33(73.3%)	9(20%)	3(6.7%)	.002
Tobacco users	35 (27.8%)	17(51.5%)	12(36.3%)	6(16.2%)	
Tobacco smoker	32(25.4%)	27(84.4%)	5(15.6%)	0(0%)	
Mix habits	14(11.1%)	4(28.6%)	6(42.8%)	4(28.6%)	
Nil					

*Body Mass Index. **Chi-square test

DISCUSSION

Body Mass Index (BMI) has shown a substantial impact on the prognosis of cancer¹¹. However, there has been a debate about the BMI indices and their magnitude of association with different cancers¹². Consequently, it is become increasingly difficult for clinicians to encourage normal BMI or recommend loss or gain of weight in patients with recently diagnosed malignancies¹³. Moreover, in this era of personalized medicine, BMI is an important factor which greatly influences treatment decision and drug dosing¹⁴. All of these parameters collectively improve the outcome in cancer patients. Hence, we have taken a step to examine the effect of BMI matrices on the prognosis of one of the most prevalent cancers in Pakistan i.e. Oral Squamous Cell Carcinoma (OSCC).

In a recent meta-analysis, Petrelli et al investigated the association of high BMI with prognosis of multiple cancers¹⁵. They found greater mortality and overall poor prognosis in patient having high BMI¹⁵. In early OSCC studies, Hu et al found that obesity is an independent risk factor for poor prognosis for oral cancer.¹⁶

Similarly, Wang and co-authors reported higher chances of recurrence and worse prognosis of OSCC in obese patients compared to the ones with normal weight¹⁷. In contrast, the phenomenon of “obesity paradox” is dominated in recent literatures⁹. It is believed that, poor nutritional intake and tumor cachexia might have contributed to low BMI documented in studies¹⁸. In present research, we found an association of low BMI with advanced stage tumor, which corroborates with recent data. Interestingly, we did not notice any correlation of BMI with tumor histology which is usually taken as less sensitive prognosticator than stage. We speculate that low frequency of cases in high grade strata are largely responsible for this discrepancy. Of note, the two prognostic indicators are distinct entities, where later is measured by the degree of keratinization. Thus, low grade encountered in an advanced stage disease is not surprising at all.

Several hypothetical reasons might explain the obesity paradox observed in our analysis. One of them is selection bias that may have occurred while stratification of patients.⁹ However, it is unlikely that this reason which fully accounts for our observation. The excess fat stores constitute the nutritional reserve of the body

which may provide an added advantage in obese patients during the time of illness.¹⁹ Hence, it is plausible that lower BMI strata in our series disproportionately includes sicker patients contributing to high rate of complications. Another important aspect of weight loss in cancer patients is subclinical tumor activity which may account for "obesity paradox" phenomenon.^{9,20} Besides that, psychosomatic factors in cancer patients could also induce weight loss by exerting negative influence on appetite²⁰.

Our clinical data indicated that mix tobacco products users were more prevalent while analyzing habits which coincides with the regional data reported in past studies.^{21,22} As most cases showed lesion originating from buccal mucosa, we speculate that the areca nut present in paan and gutka, which are gaining popularity in our population is likely responsible for the abrasion to the oral lining and inflicted carcinogenic particle to adhere and traumatized the mucosa²³. This continuous local irritation by carcinogen could lead to injury-related chronic inflammation, oxidative stress and cytokine production subsequently producing malignancy²².

Interestingly the correlation of BMI with habits showed a significant relationship of low BMI with consumers of mix tobacco products. We believe loss of weight in consumers of mix tobacco products could be confounded by other comorbidities. We thus recommend more research to evaluate this relationship.

Another important aspect of present research is that decrease BMI is more frequently encountered in elderly patients. We suspect that poor nutritional status in this age group is responsible for our observation. Furthermore, we noted male predominance in our series which is in line with the reported literature²⁴. Despite high frequency of elder men in our research, we were unable to register significant statistical link with increasing age and gender. We suggest that growing prevalence of OSCC in younger men might have subdued the aged strata causing stratification bias and insignificant statistical difference.

Strength: The present research highlighted the importance of BMI in cancer and add to the growing literature in the field of oncology. Our findings regarding the impact of BMI on outcome of OSCC is indeed a way forward towards intervention and development of prevention strategies for one of the most prevalent tumors in Pakistan. We have attempted to answer the complex question of "right" BMI in cancer to improve prognosis. Moreover, we have also investigated the influence of independent risk factors of OSCC on BMI, which is the missing aspect in many past studies.

Limitations: There are certain limitations in this study. Firstly, small sample size might have affected the reliability of our results and contributed to inconclusive inferences for some parameters. Secondly, we were restricted to BMI for assessing the relationship of obesity paradox with tumor prognosticators and other factors such as; lean body mass and fat mass which might also influence body composition was not considered. Lastly, several confounders could have biased our findings due to cross-sectional study, hence a cohort would be more useful in assessing the true impact of BMI on severity of disease.

CONCLUSION

In conclusion, our study suggested that low BMI is an important factor which might contribute to poor outcome in oral squamous cell carcinoma (OSCC). As weight loss seems indicate poor prognosis, it is imperative to avoid "obesity paradox" in order to sustain the safety and efficacy of treatment. Our findings will pave the path for necessary lifestyle interventions to optimize the standard of care for oral cancer which eventually improves the prospects of survival among patients.

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