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Role of Pro-Inflammatory cytokines IL-1-Beta in Tobacco/Pan-Masala induced Oral carcinoma and Oral submucosal fibrosis

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ABSTRACT

Introduction -The maximum occurrence of Oral squamous cell carcinoma (OSCC) is found in India due to the majority of habits like chewing tobacco, intake of betel quid and areca-nut, all are the most important risk factors presence of several cytokines, including IL- 1β, IL- 6, and IL- 8, are also related with OSCC.

Aim-The aim of this study was to investigate the correlation between the serum levels of IL-1beta in oral cancer and pre-cancer condition patients and the biological characteristics of the tumor as well as the clinic pathological status of the patients.

Methods and materials-This study was approved by the Scientific Advisory Committee and Institutional Ethical Committee of Eras Lucknow Medical university. The recruitment of study 30 Patients done at department of dentistry, Eras Lucknow Medical College and Hospital, Blood (serum) samples from patients with OSCC and oral submucosal fibrosis (OSMF) were collected before any treatment. Concentrations of serum IL-1beta were quantified by commercially available ELISA.

Results-In this research we have found that expression of inflammatory cytokine il-1beta is more signification in OSCC patient rather than OSMF patients remains contradictory.

Discussion-Recent researches also recommend that the level of IL-β in serum is significantly higher in cancer patients compared to healthy controls, especially oral cancer. Furthermore, IL-1β is more detectable in OSCC than OSMF, in blood serum, suggesting that serum serves as a good biological fluid for assessing changes in IL-1β levels.

Conclusion-IL-1β assumed cancer progression biomarker. Ongoing research development of such a method will have profound impact on cancer screening and the early diagnosis of cancers.

Keywords: IL-1Beta, OSCC, OSMF, Inflammatory Cytokines.

INTRODUCTION

Oral squamous cell carcinoma is the 6th most common malignancy throughout the worldwide for males and females, respectively, with a prevalence of oral squamous cell carcinomas (OSCC) 1-3. The maximum occurrence of OSCC is found in India due to the majority of habits like chewing tobacco, intake of betel quid and areca-nut, all are the most important risk factors 4. According to research of The Gujarat Cancer & Research Institute Registry, the situation is worst in Gujarat because 53.65% in males and 15.64% in females of all carcinomas are found to be Tobacco Related Cancers (TRCs) 5. Despite the current developments in primary treatments, the 5 year of existence rate after treatment remains

inadequately low at about 15-50% for the past 3 decades 5-9. The subsequent poor prognosis is remaining to a small response rate to existing therapeutic strategies, late-stage diagnosis, higher risk of primary site reappearance and aggressive metastasis to loco-area lymph nodes, strongly expressive of a need to improve for the diagnostic abilities and treatment efficiency. whereas Oral submucous fibrosis (OSMF) is a deceptive chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by and or associated with vesicle formation, it is always associated with juxta-epithelial inflammatory response followed by a fibroelastic change of the lamina propria, with epithelial atrophy leading to changes and stiffness of the oral mucosa, causing trismus and incapability to eat 10. Mortality rate is nearly significant because it transforms into oral cancer, particularly squamous cell carcinoma at a rate of 7%– 30% 11. The cytokine network and triggered innate immunity during the inflammation response can account for malignant transformation in OSCC12. The constitutional activation of the nuclear factor kappa B (NF- κB), a hallmark of inflammatory responses, and the presence of several cytokines, including IL- 1β, IL- 6, and IL- 8, are also related with OSCC 13. All of These inflammatory cytokines are also involved in metastasis of lymph node and indicates poor prognosis in patients with OSCC 14,15. Increasing signals has shown that IL- 1β is one of the most critical proinflammatory cytokine involved in pathogenesis of tumour 16,17. Two dissimilar signals are crucial for the initiation and secretion of IL- 1β. The first indicator upregulates the expression of pro- IL- 1β by activating NF- κB, whereas another signal stimulates the alignment of inflammasomes and activation of caspase- 1 or - 5, which encourages the cleavage of pro- IL- 1β to produce active IL- 1β for secretion. In some cases, pro- IL- 1β is not started without the occurrence of an inflammasome in the same cell. some cancer types, IL- 1β eradicates malignant cells by stimulating anticancer immunity and increasing the properties of chemotherapy. However, IL- 1β may favour tumour development and progression by creating a microenvironment that confers survival advantages to tumour cells or through autocrine signalling. The purpose of this research is to investigate the mechanisms by which tobacco induced carcinogen exposure may contribute to OSCC and OSMF to assess the potential tumour- promoting role of IL- 1β in this human malignancy. We also established that the pro- tumorigenic effects of IL- 1β in OSCC are likely through stimulating an oncogenic network of inflammatory cytokines in the tumour microenvironment whereby increasing angiogenesis, tumor progressiveness and invasiveness.

Materials and Methods

This study was approved by the Scientific Advisory Committee and Institutional Ethical Committee of Eras Lucknow Medical university. According to ethical ideologies, including the history of patients written and informed patient's consent was obtained from all the study participants before drawing blood and collecting serum.

Study Subjects recruitment

The recruitment of study Patients were done at department of dentistry, Eras Lucknow Medical College and Hospital, Lucknow during August 2015to December 2016. Study subjects were recruited by professionally trained, well skilled and experienced Oral Pathologists. The demographic and clinical details and information on previous history also were collected.

EXCLUSION AND INCLUSION CRITERIA FOR STUDY SUBJECTS

Oral squamous cell carcinoma (OSCC) group

Sample was collected from total of 40 subjects, out of which 10 were excluded for various reason, either non-confirmed OSCC by tissue biopsy (intercessional) or had other general illness apart from OSCC. Total 30 Subjects were recruited with the following eligibility criteria: ages 21–80, male or female, comprised of 20 patients who had oral squamous cell carcinoma (OSCC) and 10 patients' symptoms of pre-cancerous, oral submucosal fibrosis (OSMF) condition which were clinically diagnosed. Patients who were not currently undergoing or having undergone any form of definitive therapy for OSCC in the form of radiation, chemotherapy or any other adjunctive treatment. Before confirming with tissue histopathological analysis, the required amount of blood serum was collected and stored. All oral

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lesions and conditions like suffering from mouth opening, mouth burning sensation,

Sample collection

Serum samples were collected between 9:00AM to1:00 PM under non stimulatory condition. Participants were asked to habit of pan-masala eating, chewing tobacco and amount of intake alcohol at least one hour before collection. Blood (serum) samples from patients with OSCC and OSMF were collected before any treatment. Following collection, the serum was immediately centrifuged to remove cell debris. Supernatants were then stored at -80ºC. 2 ml of peripheral blood were drawn from all study subjects through vein puncture. Blood was transferred to an empty vial. Serum was then collected by centrifuging the coagulated blood and stored at -80ºC until further use.

IL-1Beta Estimation

Concentrations of serum IL-1beta were quantified by commercially available ELISA kit (The assay was carried out according to the manufacturer's instruction. Briefly, the kit was based on sandwich ELISA method and procedure is as follows; to the precoated IL-1beta antibody microplate, standards and sample were added, incubated (for 2 hours) and washed with buffer. To the washed plate detection antibody bound with HRP conjugate was added. After that unbound antibody was washed and a chromogen substrate was added to the wells resulting in the advanced growth of a blue colored complex with the conjugate. The development of color was stopped when addition of stop solution turning the resultant final yield (yellow in color). The intensity of color developed is proportional to the IL-1beta present which was measured in a microplate reader (BIORAD ELISA plate reader) at a wavelength of 450nm. The optical density attained was then used for calculation of IL-1beta present in each sample. The range of detection was given kit from a minimum of 5pg to a maximum of 200 pg/ml. The results were expressed as pg/ml of serum.

Statistical analysis

All statistical analyses were carried out using Graph Pad Prism for Windows ver. 5 (GraphPad Software, San Diego, CA, USA) and the statistical software program SPSS 18.0 (PASW statistics). Data were expressed as mean ± SD. A value of $P<0.05$ was considered statistically significant. Nonparametric Mann–Whitney U tests were performed to find the significance of the observed differences between groups. The area under the curve presented a direct measure of the diagnostic accuracy of the test.

Clinical Features

Demographic and clinical characteristic of the patients are outlined. premalignant lesions which consisted 10 each of OSMF and 20 OSCC subjects were included. All the premalignant and OSCC subjects either had tobacco/pan chewing/smoking or alcohol intake habits. The premalignant lesion was from buccal mucosa, vestibule together in buccal mucosa and vestibule, alveolar mucosa, palate, tongue. Similarly, the OSCC lesion was from buccal mucosa, alveolar mucosa, palate, tongue and lip. Based on the histopathological grading of OSCC, 21patients had well differentiated, 9 had moderately differentiated and zero patients was poorly differentiated lesion.

IL-1beta levels based on histological grading

For 20 patients with OSCC, IL-l-1beta concentrations were compared according to histological differentiation the median and interquartile range of serum IL-1beta concentration pg/ml for well differentiated, moderately differentiated (MD) lesions, respectively. Surprisingly, in serum IL1beta a significant down regulation was observed with well differentiated compared to and moderately differentiated. Contrarily, serum IL-1beta concentration did not show any significant difference between the histological grading in OSCC. No significant difference was evident for serum concentration in PML group based on histological grading.

Results

During this research study were identified total 30 patients aged under 25-75 years with 20 of OSCC and 10 of OSMF in the institutions surveyed. Patients of OSCC visit our hospital in advanced stage and many of them have also palpable regional lymph node. Histological grading quite often fails to indicate the actual types of lesion and its relationship with metastasis of these 20 patients, with mean value (47.9000) met the inclusion criteria. Patients with different clinical grades were also included in this study with different mean value, 3 patients were in

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clinical grade 1 (10.0%), 8 were in Grade II mean was (26.7%), 14 were Grade III with mean (46.7%), and 5 were in Grade IV with their mean (16.7%).Regarding the social habits,17 (56.7%) reported smoking and 8 (26.7%) alcohol ,23 was tobacco consumption mean was (76.7%). The mean age of the control group patients was 63.14 years (± 8.62), ranging from 50 to 84 years. Males were 24 (78.57%) and 6 (20.0%) were female. According to the habits, 23(76.7%) reported cases of Tobacco and 8 (26.7%) alcohol consumption and pan-masala were 12 and mean value was (40.0%). Mean Value of Pathological grades showed that as Pathological Grade increases mean Il-1betaconcentration in serum increases. Mean IL-1betaconcentration of Moderately Differentiated 9 patients (30.0%), 21of well differentiated (70.0%), respectively. In this study we found that significant corelation between inflammatory cytokine IL-1beta is more expressive in OSCC patients compare to OSMF cases.

Table-1

		IL-1 BETA		
		OSCC	OSMF	Total
Age intervals	25 to 35 years	3 15.0%	4 40.0%	7 23.3%
	36 to 50 years	9 45.0%	2 20.0%	11 36.7%
	51 to 65 years	8 40.0%	2 20.0%	10 33.3%
	Above 65 years	0 .0%	2 20.0%	2 6.7%
Total		20 100.0%	10 100.0%	30 100.0%

Applied χ^2 test for significance. χ^2 value=7.722; p-value=0.052; consider near to significant.

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Table2.

		IL-1 BETA		
		OSCC	OSMF	Total
Sex	Male	17 85.0%	7 70.0%	24 80.0%
	Female	3 15.0%	3 30.0%	6 20.0%
Total		20 100.0%	10 100.0%	30 100.0%

Applied fisher exact test for significance. p-value=0.372; consider not significant.

Figure 2: Graphical data showing the significant percentage values of gender with OSCC and OSMF groups. 85.0% male were suffering from OSCC while 70.0% male were with OSMF. In female graph indicating that nearly 15.0 % female with OSCC and 30.0 % female suffered with OSMF.

Table-3

		IL-1 BETA		
		OSCC	OSMF	Total
Clinical Grade	Grade I	2 10.0%	1 10.0%	3 10.0%
	Grade II	4 20.0%	4 40.0%	8 26.7%
	Grade III	11 55.0%	3 30.0%	14 46.7%
	Grade IV	3 15.0%	2 20.0%	5 16.7%
Total		20 100.0%	10 100.0%	30 100.0%

Applied χ^2 test for significance. χ^2 value=1.993; p-value=0.574; consider not significant.

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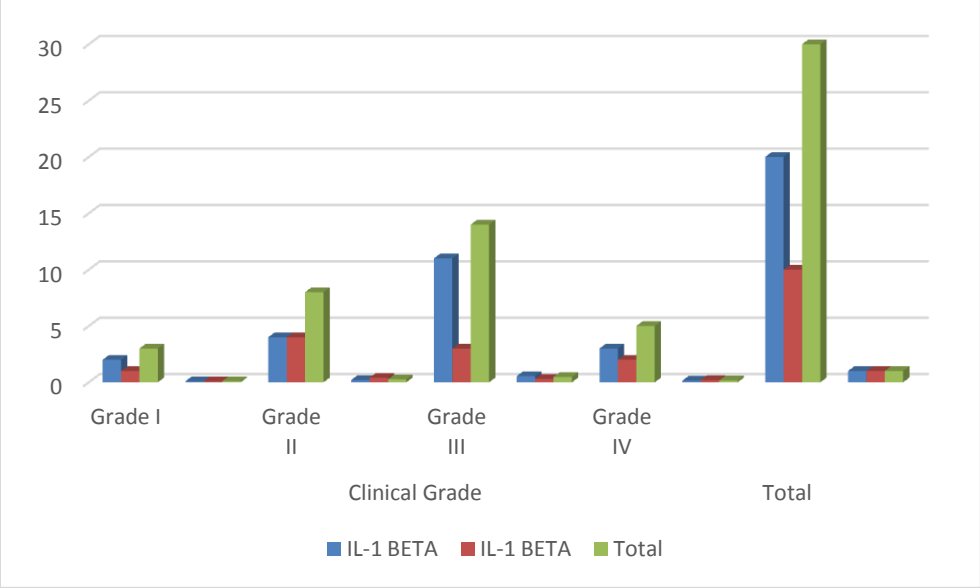

Table-4

		IL-1 BETA		
		Positive	NEGATIVE	Total
Pathological Grade	MODERATLY DIFFERENTIATED	6 30.0%	3 30.0%	9 30.0%
	WELL DIFFERENTIATED	14 70.0%	7 70.0%	21 70.0%
Total		20 100.0%	10 100.0%	30 100.0%

Applied χ^2 test for significance. χ^2 value=0.000; p-value=1.000; consider not significant.

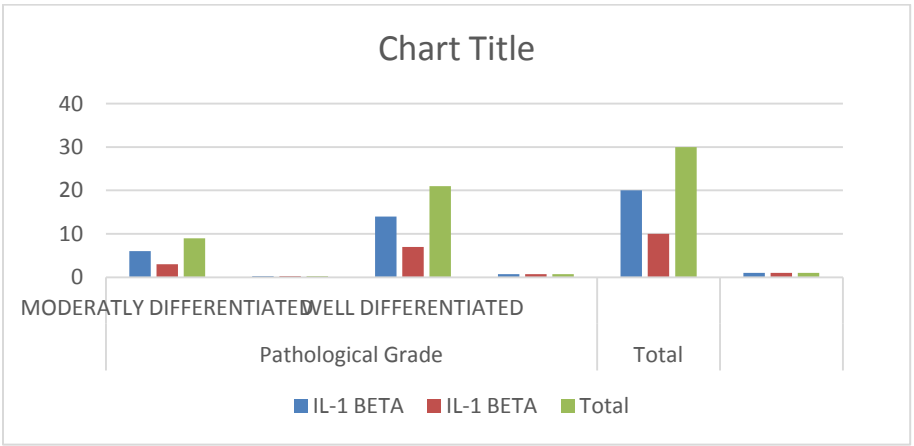

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Table-5

		IL-1 BETA		
		Positive	NEGATIVE	Total
Tobacco	Yes	17 85.0%	6 60.0%	23 76.7%
	No	3 15.0%	4 40.0%	7 23.3%
Total		20 100.0%	10 100.0%	30 100.0%

With respect to tobacco chewing study was performed on OSCC and OSMF patients, Statistical data illustrated that 17 (85.5%) patients were tormenting from OSCC and 6 (60.0%) patients tormenting from OSMF,by all of 0 patients.

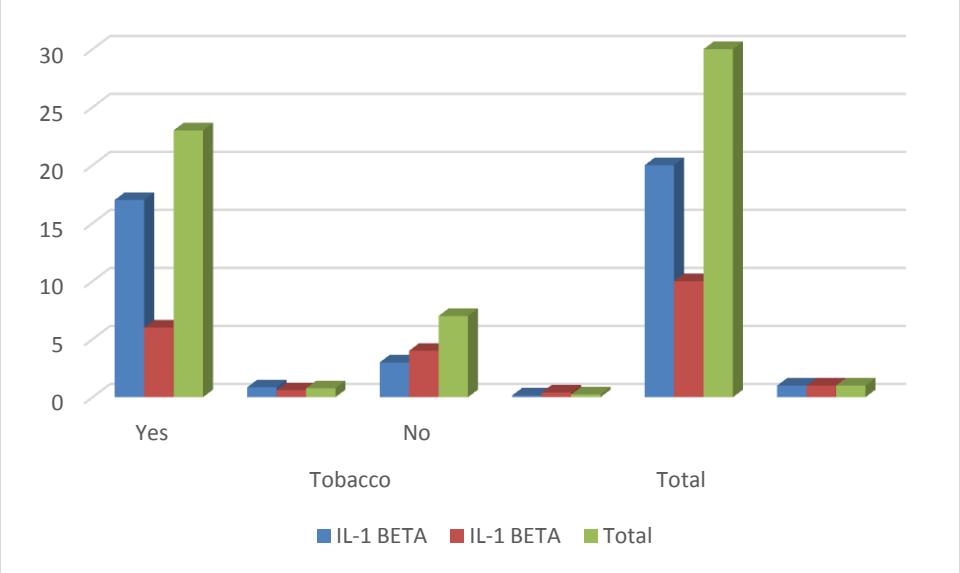

Table-6

		IL-1 BETA		
		OSCC	OSMF	Total
Smoking	Yes	12 60.0%	5 50.0%	17 56.7%
	No	8	5	13

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	40.0%	50.0%	43.3%
Total	20	10	30
	100.0%	100.0%	100.0%

Applied fisher exact test for significance. p-value=0.705; consider not significant.

The analysis was conducted over habit of smoking and it was inferred from statistical data that 12(60.0%) patients were anguishing from OSCC and 5 (50.0%) patients were anguishing from OSMF, by the whole of 30 patients

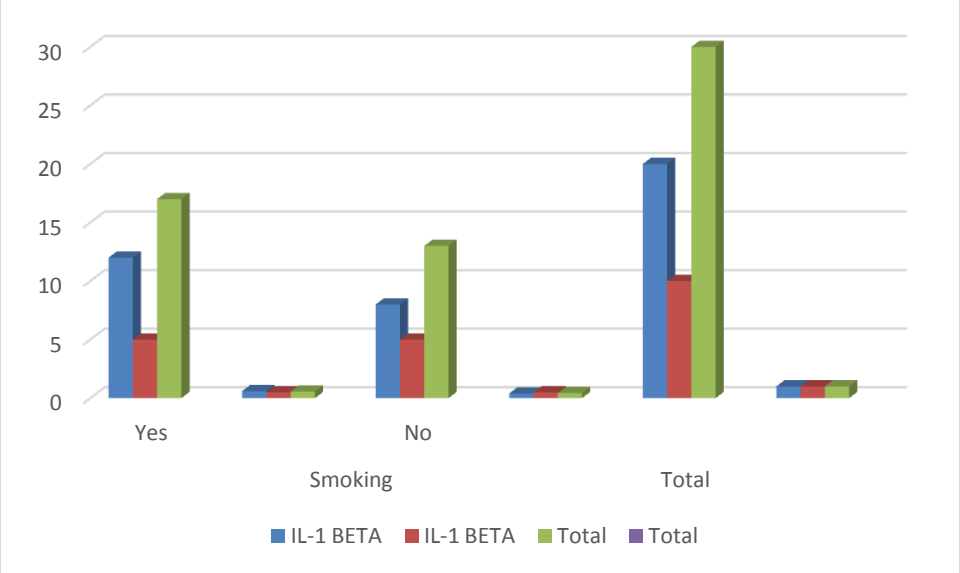

Table-7

		IL-1 BETA		Total
		OSCC	OSMF	
Panmasala	Yes	7	5	12
		35.0%	50.0%	40.0%
	No	13	5	18
		65.0%	50.0%	60.0%
Total		20	10	30
		100.0%	100.0%	100.0%

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Applied fisher exact test for significance. p-value=0.461; consider not significant.

The analysis was conducted over habit of pan masala chewing and it was inferred from statistical data that 7 (35.0%) patients were anguishing from OSCC and 5 (50.0%) patients were anguishing from OSMF, by the whole of 30 patients.

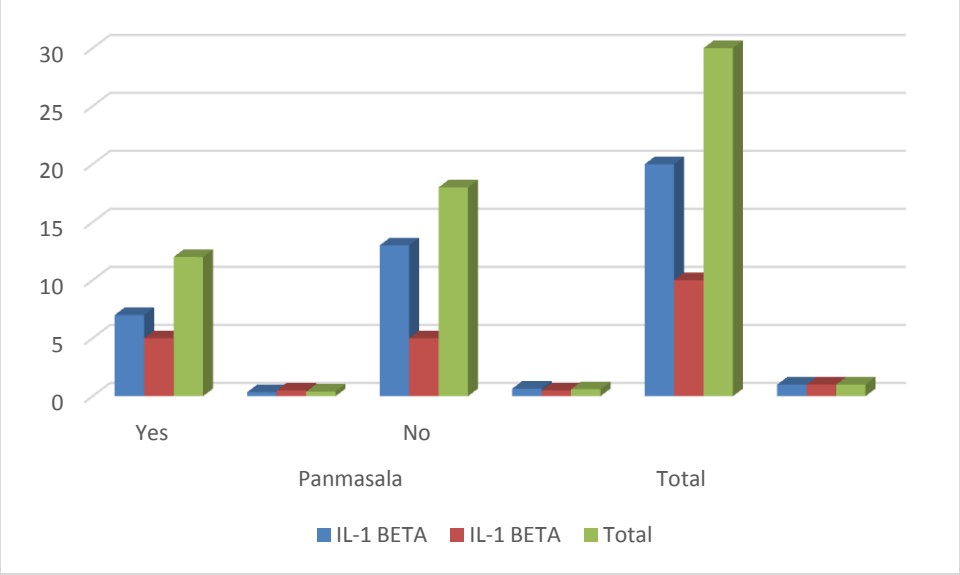

Table 8

		IL-1 BETA		Total
		OSCC	OSMF	
Alcohol	Yes	3 15.0%	5 50.0%	8 26.7%
	No	17 85.0%	5 50.0%	22 73.3%
Total		20 100.0%	10 100.0%	30 100.0%

Applied fisher exact test for significance. p-value=0.078; consider not significant.

The analysis was conducted over habit of intake of chewing and it was inferred from statistical data that 3(15.0%) patients were anguishing from OSCC and 5 (50%) patients were anguishing from OSMF, by the whole of 30 patients

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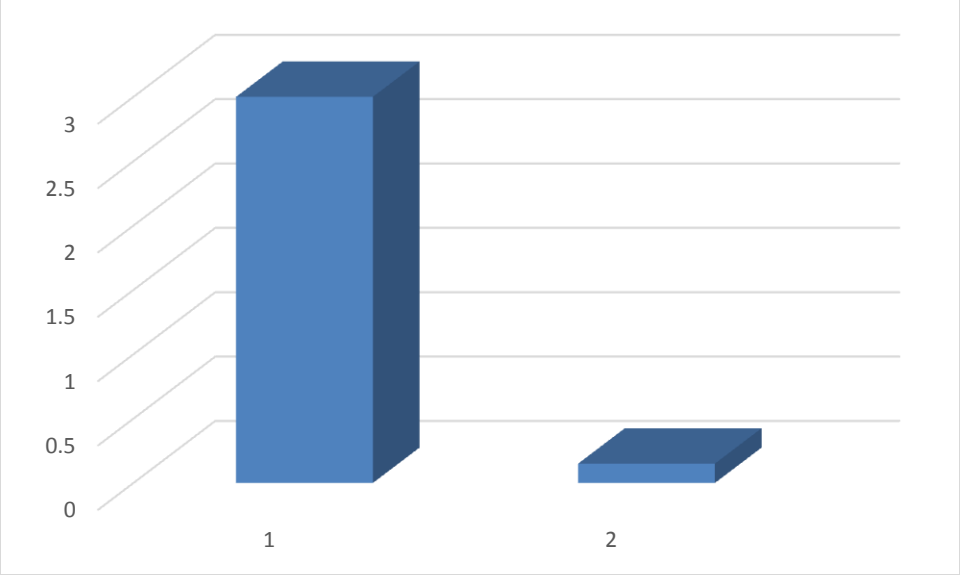
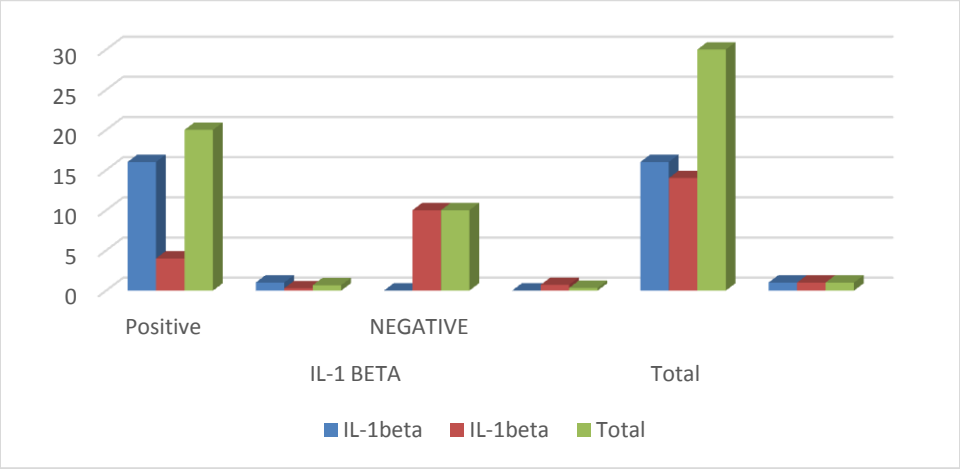


Table-9

		IL-1beta		Total
		OSCC	OSMF	
IL-1 BETA	Positive	16	4	20
		100.0%	28.6%	66.7%
	NEGATIVE	0	10	10
		.0%	71.4%	33.3%
Total		16	14	30
		100.0%	100.0%	100.0%

Applied fisher exact test for significance. p-value=<0.001; consider highly significant.



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Discussion

IL-1β is well known as an effective marker of process of carcinogenesis17. The possible molecular mechanisms by which IL-1β can encourage development of tumor and. However, to date, there has been no well elaborate study examining the levels of IL-1β at different grades and stages of cancer, in case of the serum section. The use of serum biomarkers has been discovered for various types of cancers in the past including salivary gland cancer,18 and cancers remote from the oral cavity such as breast and pancreatic cancer 19. Moreover, several researchers has reported that serum constituents can distinguish oral and systemic types of cancers (eg, lung cancer, breast cancer, pancreatic cancer, and ovarian cancer). Although there have been numerous studies that explored different types of inflammatory cytokines and chemokines as useful biomarkers for early diagnosis and progression of cancer or tumor cells, restricted amount of research has been done to investigate the relationship between IL-1β and cancer. Recent researches also recommend that the level of IL-β in serum is significantly higher in cancer patients compared to healthy controls, especially oral cancer. Furthermore, IL-1β is more detectable in OSCC than OSMF , in blood serum, suggesting that serum serves as a good biological fluid for assessing changes in IL-1β levels.20-22. IL-1β changes in different cancers will shed light on linking the possible role of inflammasomes in cancer pathogenesis, a field that has gained attention among immunologists in the past years. To detect the cancer progression biomarker, especially in serum, can be hopefully predict the progress of the carcinogenesis and allow a more modified anticancer treatment to be given to the patient.

Conclusion

Current research has identified deregulated cytokines, such as IL-1β, in some cancers mentioned above. Strong and reproducible methods for the assessment of IL-1β in serum, and the possibility of a rapid serum test as an indicator of disease and risk of malignancy are important to qualify IL-1β as a putative cancer progression serum biomarker. Ongoing development of such a method will have profound impact on cancer screening and the early diagnosis of cancers, potentially resulting in early treatment and a decrease in the high levels of morbidity and mortality associated with different types of cancers. Future aspects studies may need to be performed using a larger patient cohort, including periodontal disease group that should be included to validate firmly IL-8 and IL-1β as protein biomarkers for OSCC. The ability to engage a high throughput platform such as the protein biomarkers detection in serum is a significant tool towards the eventual utilization of serum as a clinical diagnostic fluid.

Future Prospective

Cytokines and their networks have proven to be beneficial in cancer therapy, however, the effect of some auspicious targets on various immune cell populations remains poorly understood. The same situation is with respect to surface cancer stem cell markers. For well-studied populations, such as immune-cells, the set and functions of surface receptors are fairly well defined, and scientifically use nearly the same sets of Cancer stem markers to identify populations by using ELISA method. However, less studied are the population of immune cells, the more diverse are the sets of determined receptors, and the more difficult it is to compare the results to identify persistent patterns. The research of changes in the function of surface marker expression of each individual immune cell population. after immunotherapy will simplify and unify the assessment of the effectiveness of therapy, as well as allow predicting the effectiveness of immunotherapy by analysing surface markers of immune cells of cancer patients.

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Conflict of interest - The authors have no conflict of interest to declare.

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