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A biplot analysis of an oral carcinoma profile for identification of association factors in Hospital Universiti Sains Malaysia (USM)

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Abstract—Study aimed at classifying related factors by biplot analysis of oral carcinoma patients at Hospital UniversitiSains Malaysia. Medical history of chosen patients treated with oral carcinoma in oral and maxillofacial surgery (OMFS) unit. Histopathology, lesion site, TNM stage, age group, and pathology variables were selected. Salivary gland lesions are very poorly differentiated, buccal mucosal lesions are well differentiated, while mouth, palate, tongue, and surface lip lesions are near to moderately differentiated. Stage II cases were mainly well-differentiated, Stage IV cases were moderately-differentiated, and Stage III cases were poorly differentiated. Most of Stage I cases are from the maxilla, Stage II is close to the salivary gland and mandible, Stage III is close to the palate, and Stage IV is associated with tongue, mouth floor and buccal mucosa. Salivary gland and mandible are the most prominent lesion sites below 30 and 50-59. Usually, tongue cancer grows at 30-39. Typical oral cancer sites are palate and buccal mucosa for patients aged 60 and 40-49. Squamous and adenoid cystic carcinoma are common in patients <30 and >60. Mucoepidermoid carcinoma was observed primarily in patients aged 40-49 to 30-39 years. Oral cancers were 78% squamous cell carcinoma and 55% oral tongue cancers. This also highlights the need for early diagnosis and oral cancer care by comprehensive institutionalised oral cancer education and risk factor awareness, particularly for teenagers.

Keywords— Biplot analysis, TNM stage, site of lesion, histopathology, pathology

1. Introduction

Cancer head and neck squamous cell carcinomas are the leading cause of mortality with incidence of half-million cases worldwide in 2008. Oral squamous cell carcinomas (OSCC) are the sixth most incessant malignant tumor [1], and is a virulent disease, with up to 50% of mortality rate [25].Oral squamous cell carcinoma can originate from several sites in the oral cavity but the most prevalent sites are the lateral border of the tongue (20-40%) and floor of the mouth (15–20%) [13]. An estimated age-standardized to Malaysian population ASR (W) of oral cancer incidence are 3.0 per 100,000, according to the World Health Organization (WHO) [9].The incidence of oral cancer was more among Indian females with the ASR 10.2/100,000. According to Oral Cancer Research and Coordinating Center (OCRCC) Malaysia data, deaths in Malaysia related to oral cancer reached 1587 or 1.55% of total deaths. Malaysia ranked 14th in the world with an age-adjusted death rate of 7.72 per 100,000 of the population (OCRCC 2017). Primarily of these oral cancers originating in the oral cavity and oropharynx, with established risk factors tobacco usage, alcohol consumption, betel chewing, and human papillomavirus (HPV) infection, and some genetic and epigenetic changes [2].Poor oral hygiene, dietary habits, and deficiency of vitamin D could play a role in carcinogenesis [14].Oral cancers have a multifactorial etiology which encompasses of smoking, tobacco use, alcohol consumption, paan, betel quid, viral stimuli, and some genetic and epigenetic changes [2].

Even though significant advancements in the field of therapeutics and diagnostics, the overall survival rate

has not shown significant improvement during the last few years [29].At present, the clinical and histopathological factors are mainly used for preparing the treatment plan and establishing the prognosis of oral cancer patients. In Kelantan, a previous study reported that the 5-year survival of oral cancer patients was 18.0%, and associated with age, gender, stage at diagnosis, and not having treatment which contributed to poor survival [34].Recently a study reported the association factors with the mortality which includes male gender (AOR=10.89; 95% CI: 1.99, 59.65; p = 0.006), alcohol consumption (AOR = 16.45; 95% CI: 1.36, 59.65; p = 0.028), late-stage (T3, T4) at presentation (AOR = 4.85; 95% CI: 1.12, 21.02; p = 0.035) and not receiving treatment (AOR = 5.88; 95% CI: 1.03, 33.61; p = 0.046) in Kelantan population [40].Nevertheless, these earlier studies have evaluated only a definitive number of risk factors that might affect prognosis, when there is a potential dearth of information on the association factors. We would like to contribute by providing more data on this matter that reflects on the local population. The study objective was to identify the associated factors through biplot analysis among oral carcinoma patients treated at the Hospital Universiti Sains Malaysia (USM), Kelantan, Malaysia.

2. Material and methods

The study was carried out by examining the medical records of a patient in the OMFS Unit (Hospital USM), from January 2011 to December 2018. The selected variables from medical reports include pathology, histopathology, site of the lesion, age group, and TNM staging were recorded as categorized data. Statistical analysis was carried out using the SPSS Version 23 and Past Software through the biplot data analysis. Biplots are a kind of exploratory graph used in statistics. It can generalization the natural association of the two-variables using a scatterplot (visualize the relationship). A biplot allows information on both studied variables to be displayed graphically. Interestingly, biplot analysis can optimally represent the distances between observations, through the closest distance, the relationships between variables can be seen clearly.

3. Results

This retrospective research included 117 patients with oral cancers, of which 67 (57.26%) were male and 50 (42.74%) were female. Table 1 summary the frequency of the site of the lesion according to the review record. Tongue having the highest frequency of 64 (54.7%) of the most recorded cases in seven years. The second highest is at buccal mucosa, 13 (11.1%).

Table 1: The most common of frequency site of lesion

	Frequency(*n*)	Valid Percent (%)
Tongue	64	54.7
Buccal Mucosa	13	11.1
Palate	9	7.7
Lip	4	3.4
From	6	5.1
Salivary Gland	14	12.0
Mandible	6	5.1
Maxilla	1	0.9

The main purpose of biplot techniques is to investigate the association (visualize the relationship) between two nominal variables graphically in a multidimensional space. Figure 1 - Figure 6, summarize the analysis

in detail according to the specific objective. The first analysis through biplot is to determine the relationship between histopathology and the site of the lesion.

Table 2: The most common frequency of pathology

	Frequency (n)	Valid Percent (%)
Squamous Cell Carcinoma	91	77.8
Mucoepidermoid Carcinoma	10	8.5
Adenoid Cystic Carcinoma	9	7.7
Acini Cell Carcinoma	3	2.6
Others	4	3.4

Table 2 present the frequency of cancer type squamous cell carcinoma (SCC) is the most commonly reported in seven years of record review. It is about 91 (77.8%). The second highest reported is on mucoepidermoid carcinoma 10 (8.5%).

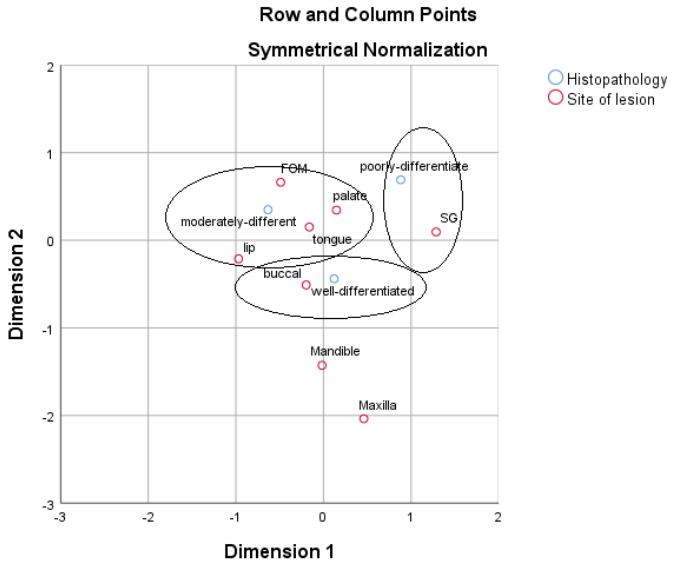

Fig. 1: Biplot analysis between histopathological differentiation and site of lesion

Figure 1 summary the finding which based on the distribution of histopathology with the site of the lesion. It was found that the salivary gland lesions are near to poorly-differentiated. Buccal mucosa lesions are near to well-differentiated while the lesions located at the floor of mouth, palate, tongue, and lip are near to moderately-differentiated. The next analysis is to determine the relationship between histopathology with TNM staging. Biplot analysis (Figure 2), summarized the stage with the histopathology. Most of the cases at Stage II were well-differentiated and those at Stage IV were moderately-differentiated. While at Stage III, the cases were of poorly-differentiated type.

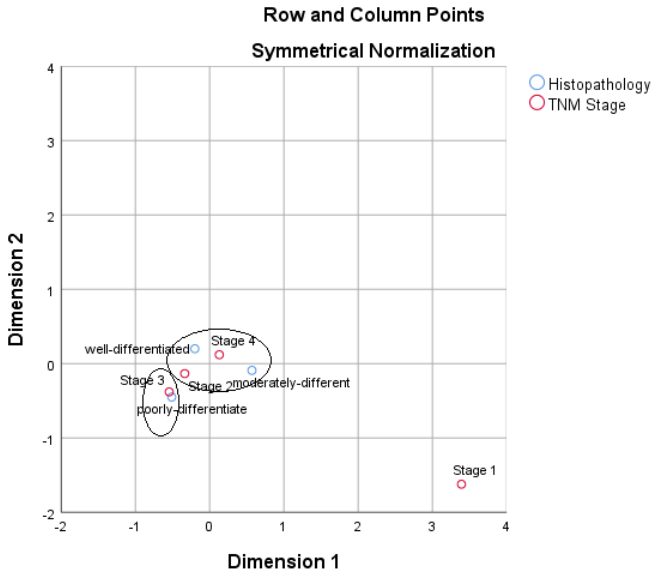

Fig. 2: Biplot analysis between histopathological differentiation and TNM staging

The next step is to discover the relationship of the site of oral cancer with the TNM stage (Figure 3). Four groups are being identified in this biplot analysis. At stage I, most of the reported cases are from the maxilla, stage II is near to salivary gland and mandible, stage III is close to the palate, and stage IV is associated with the tongue, the floor of the mouth, and buccal mucosa.

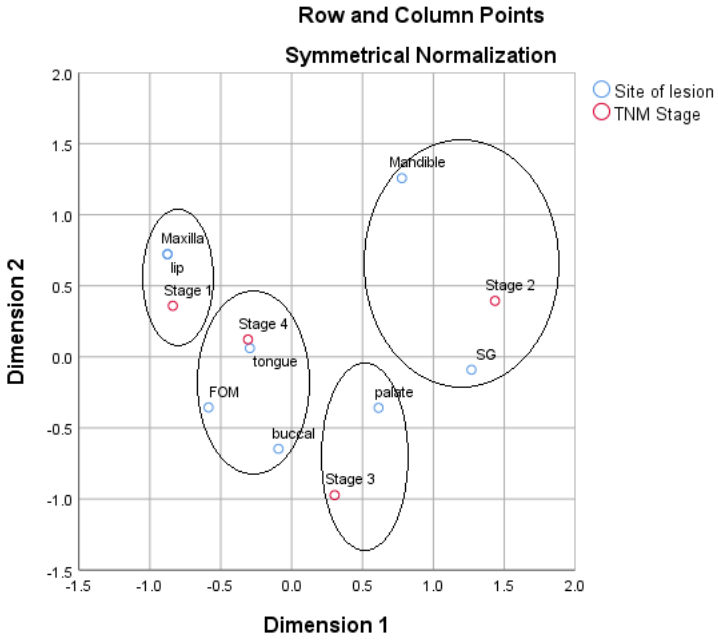

Fig. 3: Biplot analysis between the site of oral cancer and TNM staging

Figure 4 shows the biplot analysis is being extended to the age group and site of oral cancer. At the age of fewer than 30 years and 50-59 years, the most common lesion is on the salivary gland and mandible. The tongue carcinoma usually occurs at the age of 30-39 years. While at the age of more than 60, and between 40-49 years, the common sites of oral cancer are palate and buccal mucosa.

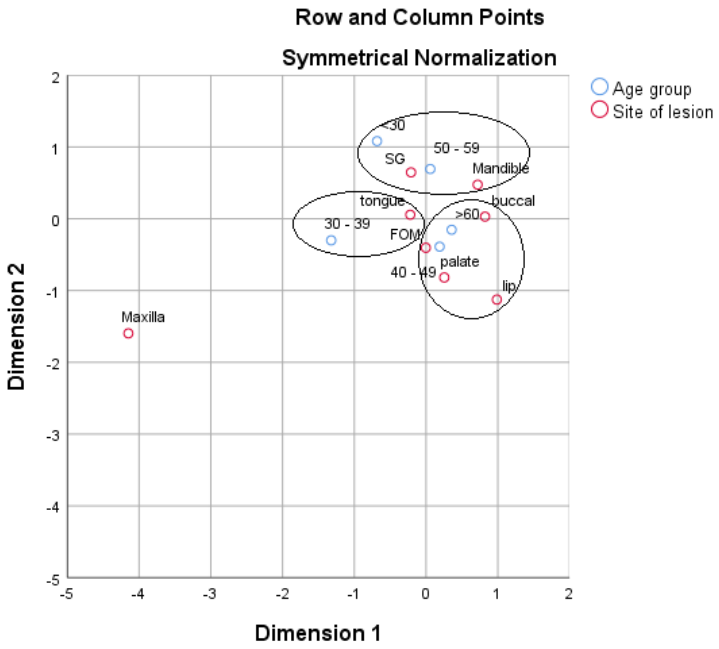

Fig. 4: Biplot analysis between the age of the group and site of oral cancer

The next biplot is to determine the association between the age of the group, and the type of oral cancer. From the biplot, it was found that squamous cell carcinoma and adenoid cystic carcinoma are more exposed to the patients which less than 30 years and greater than 60 years. Mucoepidermoid carcinoma and other mostly found in patients age 40-49 years and 30- 39 years. Figure 5 shows the detailed result of the age group with pathology.

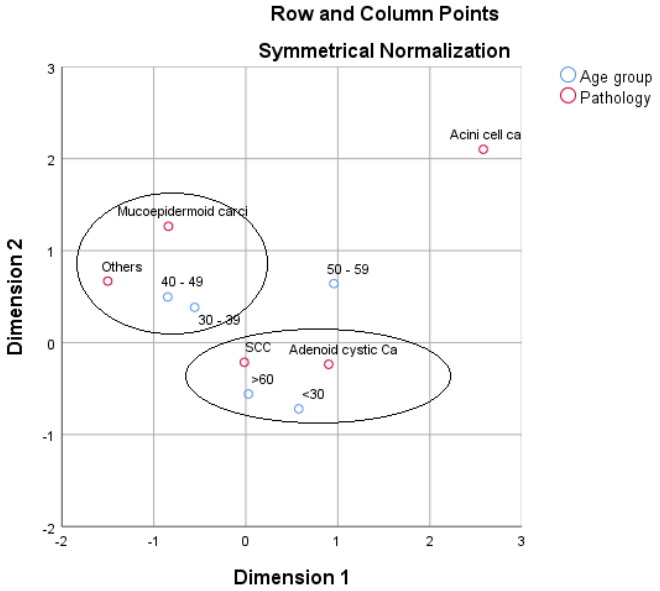

Fig. 5: Biplot analysis between the age of group and pathology

The sixth objective of the study was to explore the relationship between the age group with TNM Stage. From the record review from January 2011 to December 2018, it was found that patients' age 30-39 years are near Stage III. At Stage IV, it was found commonly among patients at the age of 40-49 years and more than 60 years. Most of the cases of Stage II are near the age of 50-59 years. The biplot analysis between the

age of the group and TNM stage was shown in Figure 6.

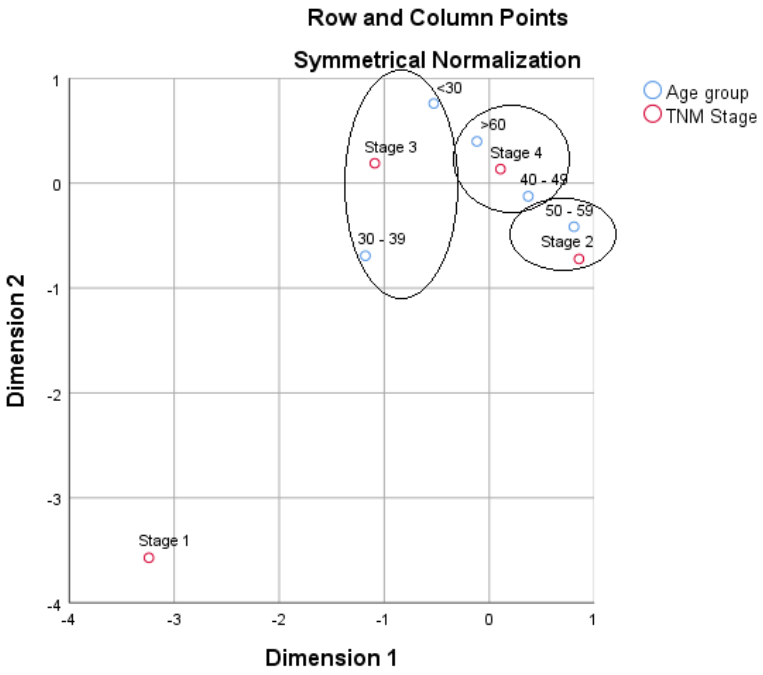

Fig. 6: Biplot analysis between the age of the group and TNM stage

4. Discussion

For decades, oral cancer has been more prevalent amongst males compared to females in many regions of the world. The findings of our study revealed that the oral cancer cases presented in our center demonstrated male predilection with the male-to-female ratio of 1.3:1. This slight male predilection prevalence is consistent with the findings from various studies [5, 7, 11]. This might due to the male patients were more exposed to tobacco consumption in the form of smoking apart from alcohol drinking.

The location with the highest frequency of oral cancer found in our study was the tongue followed by buccal mucosa. The cases involving tongue constituted more than 50% of the total cases. The finding is a similar with multicenter studies done by Dhanuthai, et al. [11]and Anis and Gaballah [3]. This phenomenon might be attributed to the frequent and long period of carcinogens mixed with saliva pooling beneath the tongue and buccal vestibules, causing these regions of the oral cavity that have thin and non-keratinized mucosa to be more susceptible to the carcinogenesis process [37].

The most prevalent oral cancer in our study is squamous cell carcinoma (SCC), with 78% of the total cases. This prevalent trend not just reported in our study, but in other several previous studies with some reported as high as more than 80% of all oral cancer in their studies [8,11,19,32, 35]. From our biplot analysis between histopathological differentiation and site of oral cancer among the oral cancer patients in our study, the salivary gland carcinoma was found to be common of poorly-differentiated type, or known as high-grade carcinoma. Buccal mucosa carcinoma was found to be more of a well-differentiated type or low-grade type, which is similar to findings by Fang, et al. [12] with 53% of the buccal mucosa carcinoma were well-differentiated type. In our study, oral cancer located at the floor of mouth, palate, tongue, and lip were common of moderately-differentiated type.

The level of histopathological differentiation was found to be inversely correlated with the oral cancer

aggressiveness and recurrence rate [12], apart from serving as a prognostic factor [21,31]. Therefore, the poorly-differentiated and moderately-differentiated tumors would have a poorer prognosis and higher recurrence rate, compared to the well-differentiated type. Thus our biplot analysis of histopathological differentiation and location of oral cancer may allow us to better assess to the prognosis and locoregional control of the patients. Several authors found that once the TNM staging of oral cancer reaches advanced stages (stage III and IV), the patients' survival rate would be reduced to less than 50% [10,20,22,26, 28]. The biplot analysis between TNM staging and histopathological differentiation in our study also reflects the advanced stages of TNM staging (stage III and stage IV) cases were more frequently found with moderately-differentiated and poorly-differentiated oral cancers, which were more aggressive with poorer prognosis.

From our biplot analysis of the relationship between sites of oral cancer and TNM staging, we also noted that the palate, tongue, buccal mucosa, and floor of mouth were usually presented as advanced staged (stage III and stage IV) cases. One of the reasons contributing to this scenario is that our center is a tertiary center of oral cancer cases referral, hence we were receiving these advanced stages of oral cancer cases from peripheral hospitals and centers. Apart from that, this finding could be due to oral cancers at these sites were mostly of moderately-differentiated tumors (as noted from our biplot analysis between the site of oral cancer and histopathological differentiation), thus leading to the more aggressive progress of the tumors [12]. Interestingly, we found out in the present study that the tongue carcinoma usually occurred among young adults in the age group of 30 to 39 years old, from our biplot analysis between age group and oral cancer site. And it is a noteworthy fact that tongue cancer constituted 55% of all the oral cancers in our study, which means tongue cancer was commonly seen among the young adults in our center. Since the 1990s, it was noted that there was a consistently-increasing trend of tongue cancer occurrences in young patients or those aged less than 45 years old [6,27,30,36, 39]. Apart from the known risk factors of tobacco product consumption and betel nut chewing at an early age, some authors demonstrated the role of viral infection, particularly the human papillomavirus (HPV), in the incidences of oral tongue cancers among the young adults [4,18, 33]. The results also showed relationship between the type of oral cancer and age group and we found squamous cell carcinoma was commonly found in 2 age groups, i.e. those 30 to 39 years old and those aged more than 60 years old. This finding is consistent with some authors' findings that those aged less than 45 years old were afflicted with squamous cell carcinoma with percentages ranging from 12.8% to 34% too, apart from the elderly patients [3,15,17,23].

The more elderly patients tend to present with advanced stage (stage III and stage IV) of oral cancer. It was found that despite the multimodality therapy employed in treating these elderly patients with advanced-stage cancer, the survival rate was less than 60% [16, 38]. We also noted a similar finding in our biplot analysis between age group and TNM staging of oral cancer, i.e. those patients aged more than 60 years old were commonly presented at stage IV cancer to our center. Nevertheless, we encountered a surprising finding whereby those aged 30 to 39 years old were frequently presented with stage III oral cancer too. This is comparable to the findings of a study done by Mahmood, et al. [23] with 33% of the patients presented at stage III and stage IV oral cancers at age less than 40 years old [23]. Nevertheless, the younger adults would have better prognosis and survival especially if the oral cancers had an association with HPV infection [24]. According to a multi-center study done by Zhang, et al. [41], it was found that the survival rates of oral cancer patients (in both young and elder patients) with advanced stage would be improved significantly if they were undergo multimodality therapy that combined surgery, radiotherapy, and chemotherapy [41].

5. Conclusion

This paper examines the relationship through the biplot analysis among the oral carcinoma. Through this analysis, some of the relationships can be visualized through the biplot analysis.

The pattern obtained from the studied factor can be used to plan further action in decision making. In conclusion, the oral cancers presented in our center were mostly squamous cell carcinoma (78%) with 55% of oral cancers occurred at the tongue. We also found that young adults commonly presented with advanced-stage oral cancer. This phenomenon portends compromise in quality of life due to morbidities associated with advanced-stage cancers in these young adults and their families. This also in turn reflects the need for early detection and management in oral cancer even in young adults through systematic institutionalized education on awareness and knowledge of oral cancer with its risk factors.

6. Conflict of interest disclosures

The authors declare no conflicts of interest.

7. Acknowledgments

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