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The Association of Ethnicity and Oncologic Outcomes for Oral Cavity Squamous Cell Carcinoma (OSCC)

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Simple Summary: Oral squamous cell carcinoma is a global health concern, particularly affecting the South Asian population. The South Asian community is among Canada's largest and most rapidly expanding minority groups. This study compared the outcomes of South Asian patients with oral squamous cell carcinoma to the general population at a Canadian cancer center. In total, 697 patients who underwent surgery for oral squamous cell carcinoma between 2009 and 2022 were evaluated, with South Asian patients constituting 9% of the cohort. Despite similar tumor characteristics and treatments, South Asian patients had double the risk of cancer recurrence and significantly worse survival compared to non-South Asian patients. Understanding the association between South Asian ethnicity and outcomes in OSCC is crucial for informing public health initiatives to meet the distinctive needs of this population, thus fostering a more inclusive and supportive environment.

Abstract: (1) Background: To compare oncologic outcomes of South Asian (SA) patients treated for oral squamous cell carcinoma (OSCC) to the general population. (2) Methods: Adult patients who underwent surgical resection of OSCC +/− adjuvant treatment between 2009 and 2022 (N = 697) at a regional cancer centre in Canada were included. SA patients, identified using a validated method, were compared to non-SA patients. Kaplan–Meier methods were used to compare the primary outcomes, disease-specific survival (DSS) and recurrence-free survival (RFS) across baseline univariate characteristics, including betel nut consumption. Median follow-up time was 36.4 months. Cox proportional hazard models were used to identify independent predictors of survival with significance set at $p < 0.05$. (3) Results: SA patients (9% of cohort, N = 64) were significantly younger and had lower rates of smoking and alcohol consumption compared to non-SA patients ($p < 0.05$). SA patients had a two-fold higher risk of recurrence and significantly worse disease-specific survival, even after adjusting for stage and high-risk features [RFS: HR 2.01 (1.28–3.14), DSS: HR 1.79 (1.12–2.88)]. The consumption of betel nut was not associated with outcomes. (4) Conclusions: SA patients had significantly worse oncologic outcomes, even after controlling for known predictors of poor prognosis. These findings are novel and can inform personalized treatment decisions and influence public health policies when managing patients with different ethnic backgrounds.

Keywords: South Asian; ethnicity; betel nut; oral squamous cell carcinoma (OSCC); oral cancer; head and neck cancer

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1. Introduction

Head and neck cancer is the seventh most common cancer worldwide, with 625,173 new cases and 323,160 deaths in 2018 [1]. Oral cavity cancers account for 30% of all head and neck cancers and 90% of these are oral squamous cell carcinomas (OSCCs) [2]. These cancers include tumors of the floor of the mouth, anterior tongue, alveolar ridge, retromolar trigone, the hard palate, and the buccal mucosa. They stand as among the most prevalent malignant neoplasms in South Asia, encompassing India, Pakistan, Bangladesh, and Sri Lanka. In 2020, these regions witnessed a staggering total of 413,583 new diagnoses and 229,633 fatalities attributed to OSCCs [3]. Furthermore, oral cancer incidence and mortality rates in South Asia are almost twice those globally [4].

There are a variety of factors that are known to contribute to the development of OSCCs, including the consumption of tobacco and alcohol, dental trauma, and human papilloma virus [5]. The predominance of OSCCs in South Asia is often attributed to the use of betel nut [6], which can be consumed in a variety of ways but is most often dried and ground into a powder and wrapped in a package known as betel quid or pan, comprised of a mixture of slaked lime, flavoring, and tobacco. Its use is influenced by social acceptability, religious beliefs, and stimulant properties. Betel quid is often stored inside the cheek for hours, similar to chewing tobacco. The slaked lime, most often used in India, is particularly problematic as it causes oxidative DNA damage and local mucosal abrasion, creating deeper exposure to the carcinogenic components [7]. The gingivobuccal region is the most commonly involved subsite in South Asia, whereas tongue and floor of mouth cancers are more common in the Western world [8]. This difference in subsite involvement likely mirrors distinctions in the etiology of OSCC between South Asia and Western populations potentially linked to their respective consumption habits, such as betel nut chewing and alcohol/tobacco use.

Although there have been improvements in the quality of life of patients with OSCC, both the disease itself as well as its treatment remain morbid, with a 5-year overall survival rate of 50 to 60% [9]. Current treatments include surgical resection, radiotherapy, chemotherapy, or a combination of these modalities. The primary treatment for early-stage (stage I and II) and advanced-stage (stage III and IV) OSCC is surgical resection of the tumor [10]. Previous North American studies have looked at the differences in head and neck cancer disease outcomes according to ethnicity, showing large disparity in mortality rates among African American versus white patients in the United States [11–13]. These differences have been attributed to a combination of tumor stage at time of presentation, access to healthcare, and exposure to carcinogens. Nichols et al. reported that even after controlling for tumor stage at time of presentation, African American patients had poorer outcomes, suggesting other intrinsic and extrinsic factors such as genetics and socioeconomic status influence survival in OSCC [14]. Arbes et al. accounted for socioeconomic status, which resulted in the elimination of the survival disadvantage observed among Black patients [15]. To date, however, there has been little research that compares oncological outcomes of patients of South Asian (SA) ethnicity with OSCCs compared to other ethnicities.

Our regional cancer centre, based in Calgary, Alberta, Canada, treats a high volume of OSCC in patients with diverse ethnic backgrounds. SA patients represent a significant proportion of patients treated. Given the increased incidence and mortality rates of patients with OSCC in India and based on the experience of the senior authors noting worsened outcomes in SA patients, the objective of this study was to characterize oncological outcomes among patients of SA ethnicity within our centre and compare these outcomes to patients with OSCC who are not of SA ethnicity. The analysis revealed that SA patients exhibited significantly poorer outcomes, even after adjusting for established predictors of recurrence and disease-specific survival. It was the intention of the study to bring to light the potential for a vulnerable population of patients that may require a unique approach to assessment and treatment.

2. Materials and Methods

2.1. Patient Selection

Adult patients (age 18 or older) that underwent curative intent primary surgical resection of OSCC at a regional cancer centre were included in the cohort. The setting of this study is that of a regional cancer centre where all head and neck cancers, both early- and late-stage, are managed by a multidisciplinary team with expert training and extensive experience. Patient data (N = 697) were prospectively collected on all consecutive patients treated at this centre, and included all patients treated between 2009 to 2022. Patients with recurrent OSCC, a second primary malignancy, a synchronous primary malignancy, or who did not receive surgery as a primary treatment modality were excluded (Figure 1). The variables collected included the following: patient demographics, risk factors (ethnicity, age, gender, smoking and alcohol status, betel nut use), pathologic data (AJCC 8th edition TNM staging [16], including presence of extranodal extension (ENE), lymphovascular invasion (LVI), perineural invasion (PNI)), and treatment (adjuvant radiation and/or chemotherapy). The study design was a retrospective cohort study, based on prospectively collected data.

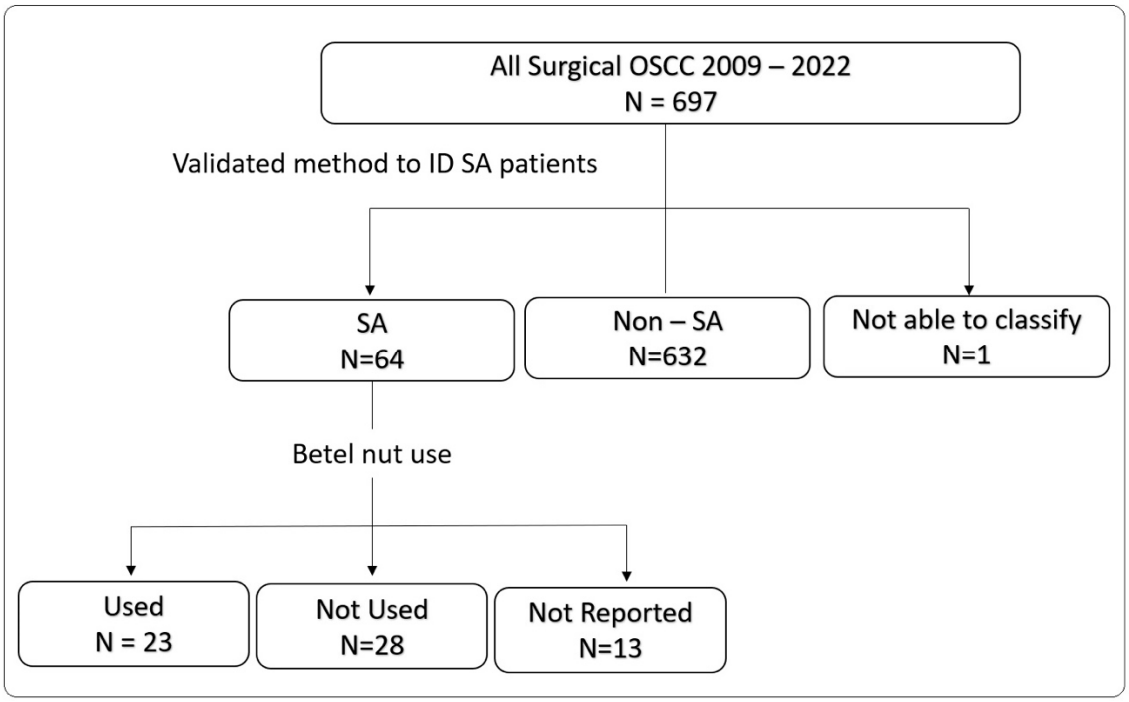


Figure 1. Patient selection.

Patients of SA descent were identified using a multistep approach. First, a previously constructed and validated SA surname list [17] was used to assign SA ethnicity to the patient population. The validated SA surname list was then linked with the patient database to generate an SA patient list. In addition, to ensure the accuracy of the cohort of SA patients, the final study cohort was manually entered into a surname's origin website [18]. This list was reviewed by two researchers with SA/middle eastern backgrounds to generate a final list of SA patients. This method has been used successfully to identify ethnic groups in other studies [19,20].

2.2. Statistical Analysis

We interrogated a prospectively collected database of all patients treated for OSCC at the Calgary regional cancer centre. Patient factors, tumor factors, treatment factors and outcomes were analyzed and compared between the SA and non-SA groups.

Categorical outcomes were compared between groups using chi-square and continuous outcomes were compared using Student's *t*-test. Primary outcomes were recurrence-free survival (RFS) and disease-specific survival (DSS). RFS was defined as time from surgery to time of last follow-up (censored) or local/regional/distant recurrence, whichever came first. DSS was defined as time from surgery to time of last follow-up (censored) or death related to OSCC. The difference in RFS and DSS between patients of SA ethnicity and those of non-SA ethnicity was determined by comparing the time-to-event (Kaplan–Meier survival curves) using a log-rank test statistic. These were censored at 3 years of follow-up, based on the literature demonstrating that recurrences are most likely to occur within 2 years of treatment [21]. Time-to-event outcomes were then adjusted for variables that potentially modified or confounded the relationship between the outcome and exposure (social habits, stage, high risk features on surgical pathology, type of adjuvant treatment) using Cox proportional hazards (PH) regression models. These variables were, in part, based on clinical relevance, having been shown in the literature to potentially modify the oncologic outcomes [22–26]. Variables that had a *p*-value of <0.20 in the univariate model were included in the multivariable model. Stepwise selection methods were used to develop the final models. A p-value < 0.05 was considered statistically significant. Owing to the prospective and rigorous nature of the data collection, missing data were infrequently seen; when missing data were encountered, these were excluded from the analysis. Betel nut consumption was not prospectively collected, but due to the published association between consumption and carcinogenesis, a chart review was performed, and where possible, betel nut consumption was collected. As a secondary outcome of the study, a sub-analysis of only patients of SA ethnicity was performed to look for an association between betel nut consumption and oncologic outcome (DSS and RFS) by comparing the time-to-event (Kaplan–Meier survival curves) of those that did and did not consume betel nut using a log-rank test statistic.

Statistical analysis was performed using Stata, version 14 [27]. This study was approved by the University of Calgary Conjoint Health Research Ethics Board.

3. Results

Using the previously described approach for selecting SA patients, we identified 64 SA patients and 632 non-SA patients, which served as the comparison group. We were unable to classify one patient as either SA or non-SA (Figure 1). Of the 697 patients that were included, 9% (N = 64) were of SA ethnicity. Table 1 describes the cohort by patient and tumor characteristics stratified by ethnicity. The median follow-up time was 36.4 months (SD = 31.02). SA patients were significantly younger and were less likely to smoke or drink. There were no differences in tumor pathologic characteristics (T-stage, N-stage, ENE, LVI, PNI), nor in the use of adjuvant radiation between the SA and non-SA patients.

3.1. Recurrence-Free Survival

Univariate Kaplan–Meier analysis revealed that patients of SA ethnicity had worse RFS [HR = 2.35 (1.51–3.65)] than those of non-SA ethnicity (Figure 2A). RFS for SA patients at 3-year follow up was 52% compared to 76% in the non-SA group ($p < 0.01$). Pathologic characteristics were significantly associated with worsened RFS on univariate analysis: advanced T-stage [HR = 2.17 (1.55–3.04)], node positivity [HR = 2.98 (1.99–4.45)], presence of ENE [HR = 5.39 (3.57–8.14)], advanced clinical stage [HR = 5.14 (2.82–9.36)], presence of LVI [HR = 2.93 (2.00–4.29)], and presence of PNI [HR = 1.78 (1.24–2.55)] (Figure 2A).

Table 1. Patient demographics.

Characteristic		Total	Non-South Asian	South Asian	*p*-Value
		N = 696	**N = 632**	**N = 64**	
Gender					ns
	Female	265 (38%)	244 (39%)	21 (33%)	
	Male	431 (62%)	388 (61%)	43 (67%)	
Age					**0.0194 ***
	Mean [SD]	62.4 [13.34]	62.8 [13.24]	58.0 [13.72]	
	Range	23.6–96.3	23.6–96.3	25.8–79.3	
Smoking History					**<0.0001 ^**
	Never Smoked	191 (27%)	153 (24%)	38 (59%)	
	Ex-smoker	258 (37%)	244 (39%)	14 (22%)	
	Current Smoker	227(33%)	216 (34%)	10 (16%)	
	Not Stated	21 (3%)	19 (3%)	2 (3%)	
Betel Nut Usage					N/A
	Yes	N/A	N/A	23 (36%)	
	No	N/A	N/A	28 (44%)	
	Not Stated	N/A	N/A	13 (20%)	
Drinking History					**<0.0001 ^**
	Never Drinker	155 (22%)	121 (19%)	34 (53%)	
	Ex-drinker	70 (10%)	66 (10%)	4 (6%)	
	Current Drinker	411 (59%)	395 (63%)	16 (25%)	
	Not Stated	60 (9%)	50 (8%)	10 (16%)	
Pathologic T stage					ns
	T0/Tis	31 (4%)	29 (5%)	2 (3%)	
	T1	234 (34%)	217 (34%)	17 (27%)	
	T2	169 (24%)	149 (24%)	20 (31%)	
	T3	83 (12%)	76 (12%)	7 (11%)	
	T4	171 (25%)	153 (24%)	18 (28%)	
	Tx	8 (1%)	8 (1%)	0 (0%)	
Pathologic N stage					ns
	N0	268 (39%)	245 (39%)	23 (36%)	
	N1	70 (10%)	64 (10%)	6 (9%)	
	N2	138 (20%)	121 (19%)	17 (27%)	
	N3	29 (4%)	25 (4%)	4 (6%)	
	Nx	186 (27%)	177 (28%)	14 (22%)	
Pathologic Clinical Stage					ns
	Stage 0	4 (1%)	3 (0%)	1 (2%)	
	Stage I	74 (11%)	70 (11%)	4 (6%)	
	Stage II	87 (13%)	77 (12%)	10 (16%)	
	Stage III	80 (11%)	73 (12%)	7 (11%)	
	Stage IV	260 (37%)	232 (37%)	28 (44%)	
	Not Stated	191 (27%)	177 (28%)	14 (22%)	
Extracapsular Spread					ns
	ECS not present	146 (21%)	131 (21%)	15 (23%)	
	ECS present	93 (13%)	81 (13%)	12 (19%)	
	N/A (eg N0 neck)	457 (66%)	420 (66%)	37 (58%)	
Lymphvascular Invasion					ns
	Absent	500 (72%)	456 (72%)	44 (69%)	
	Present	112 (16%)	102 (16%)	10 (16%)	
	Not Stated	84 (12%)	74 (12%)	10 (16%)	
Perineural Invasion					ns
	Absent	403 (58%)	363 (57%)	40 (63%)	
	Present	202 (29%)	185 (29%)	17 (27%)	
	Not Stated	91 (13%)	84 (13%)	7 (11%)	
Treatment					ns
	Surgery Alone	427 (61%)	389 (62%)	38 (59%)	
	Surgery + Radiation	180 (26%)	166 (26%)	14 (22%)	
	Surgery + Chemoradiation	89 (13%)	77 (12%)	12 (19%)	

^ Wilcoxon rank-sum test; * Fisher's exact test; ns = not significant.

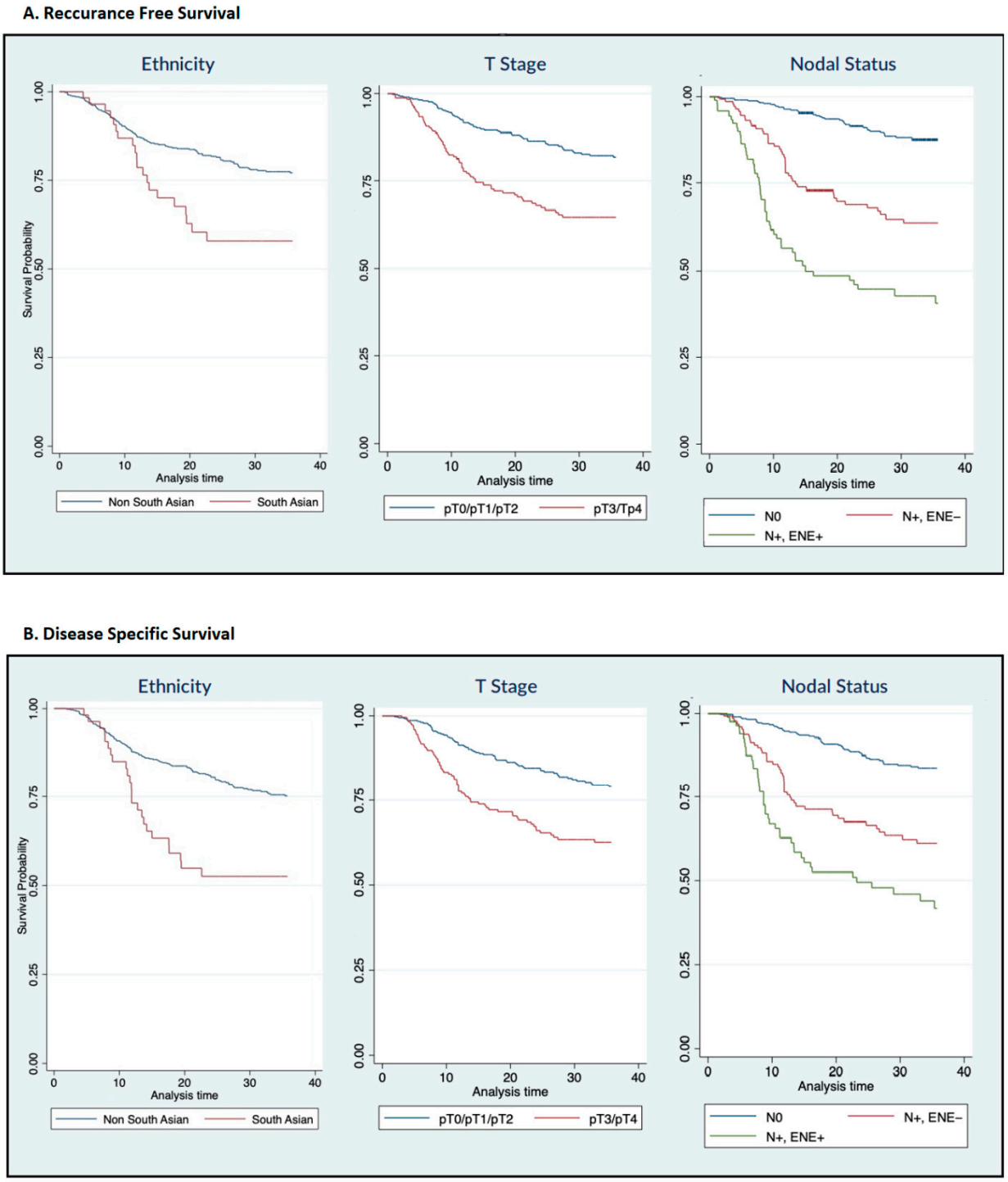


Figure 2. (**A**) Recurrence-free survival and (**B**) Disease-specific survival stratified by univariate factors. (N0 = no metastatic lymph nodes, N+ = positive lymph node metastases, ENE = lymph node metastases with extranodal extension).

After adjusting for the above-mentioned covariates on multivariable analysis, SA ethnicity [HR = 2.01 (1.28–3.14)], advanced T-stage [HR = 1.46 (1.02–2.10)], nodal positivity [HR = 2.65 (1.77–3.99)], and presence of ENE [HR = 4.32 (2.75–6.78)] were all associated with worsened RFS (Table 2).

Table 2. Cox regression analysis for recurrence-free survival.

	Univariate Analysis		Multivariable Analysis	
Variable	**Hazard Ratio [95% CI]**	***p*-Value**	**Hazard Ratio [95% CI]**	***p*-Value**
Ethnicity, non-SA vs. SA	2.35 [1.51–3.65]	<0.0001	2.01 [1.28–3.14]	**0.002**
Pathologic T Classification, pT0-pT2 vs. pT3-pT4	2.17 [1.55–3.04]	<0.0001	1.46 [1.02–2.10]	**0.04**
Pathologic Node Positivity, pN0 vs. pN+	4.81 [3.08–7.51]	<0.0001	–	–
Clinical Stage, I/II vs. III/IV	5.14 [2.82–9.36]	<0.0001	–	–
Lymphovascular Invasion, no vs. yes	2.93 [2.00–4.29]	<0.0001	–	–
Perineural Invasion, no vs. yes	1.78 [1.24–2.55]	0.002	–	–
Extracapsular Spread (ref: N0)				
N+, ECS−	2.98 [1.99–4.45]	<0.0001	2.65 [1.77–3.99]	**<0.0001**
N+, ECS+	5.39 [3.57–8.14]	<0.0001	4.32 [2.75–6.78]	**<0.0001**
Treatment Modality (ref: Surgery Alone)				
Surgery + Radiation	2.30 [1.57–3.36]	<0.0001	–	–
Surgery + Chemoradiation	2.84 [1.83–4.34]	<0.0001	–	–

3.2. Disease-Specific Survival

On univariate Kaplan–Meier analysis, SA ethnicity was associated with worsened disease-specific survival [HR = 2.14 (1.34–3.42)]. DSS for SA patients at 3-year follow up was 59% compared to 77% in the non-SA group ($p < 0.01$). Other negative prognostic features included the following: advanced T-stage [HR = 2.37 (1.66–3.36)], nodal positivity [HR = 3.70 (2.38–5.74)], presence of ENE [HR = 8.04 (5.24–12.35], advanced clinical stage [HR = 7.67 (3.73–15.78)], presence of LVI [HR = 3.11 (2.11–4.57)], and presence of PNI [HR = 2.20 (1.53–3.18)] (Figure 2B).

After adjusting for the above-mentioned covariates on multivariable analysis, SA ethnicity [HR = 1.79 (1.12–2.88)], advanced T-stage [HR = 1.64 (1.10–2.43)], node positivity [HR = 3.97 (2.44–6.45)], and presence of ENE [HR = 16.40 (9.00–29.91)] predicted worsened DSS (Table 3).

Table 3. Cox regression analysis for disease-specific survival.

	Univariate Analysis		Multivariable Analysis	
Variable	**Hazard Ratio [95% CI]**	***p*-Value**	**Hazard Ratio [95% CI]**	***p*-Value**
Ethnicity, non-SA vs. SA	2.14 [1.34–3.42]	0.001	1.79 [1.12–2.88]	**0.016**
Pathologic T Classification, pT0-pT2 vs. pT3-pT4	2.37 [1.66–3.36]	<0.0001	1.64 [1.10–2.43]	**0.015**
Pathologic Node Positivity, pN0 vs. pN+	6.10 [3.75–9.92]	<0.0001	–	–
Clinical Stage, I/II vs. III/IV	7.67 [3.73–15.78]	<0.0001	–	–
Lymphovascular Invasion, no vs. yes	3.11 [2.11–4.57]	<0.0001	–	–
Perineural Invasion, no vs. yes	2.20 [1.53–3.18]	<0.0001	–	–
Bone Invasion, no vs. yes	1.80 [1.11–2.92]	0.017	–	–
Extracapsular Spread (ref: N0)				
N+, ECS−	3.70 [2.38–5.74]	<0.0001	3.97 [2.44–6.45]	**<0.0001**
N+, ECS+	8.04 [5.24–12.35]	<0.0001	16.40 [9.00–29.91]	**<0.0001**
Treatment Modality (ref: Surgery Alone)				
Surgery + Radiation	2.28 [1.53–3.41]	<0.0001	0.85 [0.53–1.36]	ns
Surgery + Chemoradiation	3.14 [2.00–4.94]	<0.0001	0.27 [0.14–0.53]	**<0.0001**

ns = not significant.

3.3. Pattern of Failure in Those That Recurred

Among the 193 patients that developed a recurrence, 86% of patients of SA ethnicity recurred either locally or regionally compared to 87% of patients of non-SA ethnicity. Conversely, 14% of patients of SA ethnicity and 13% of patients of non-SA ethnicity had distant recurrence. The difference in pattern of failure was not significant.

3.4. Betel Nut Use in SA Patients

A chart review of the 64 SA patients revealed that 23 used betel nut, 28 did not use betel nut, and 13 did not have betel nut use reported. Univariate analysis of just the SA patients did not predict a difference in RFS or DSS between those who used betel nut and those who did not (Figure 3).

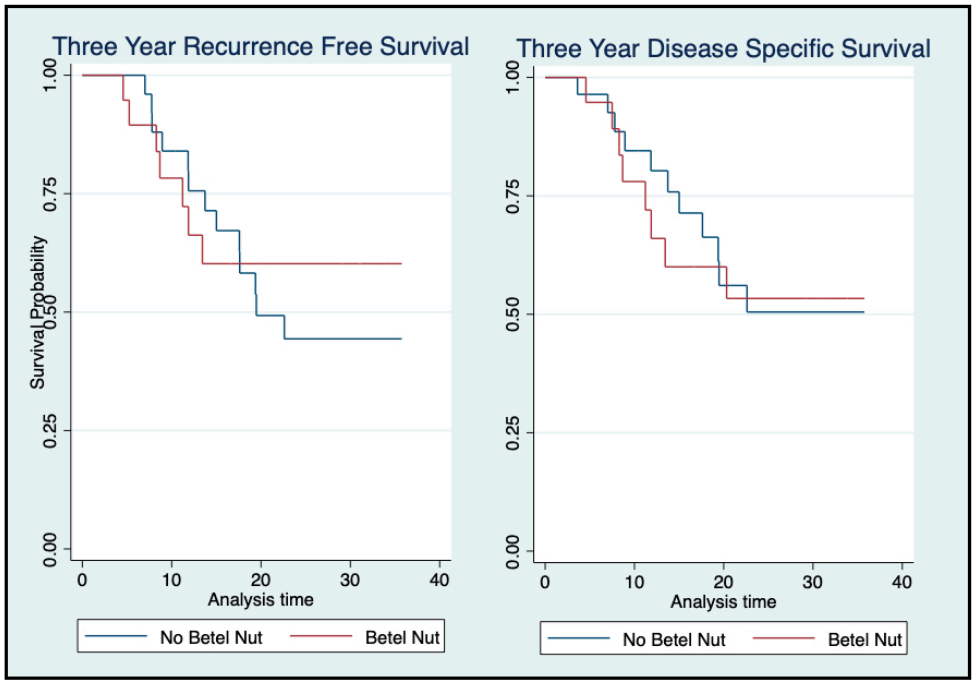


Figure 3. Recurrence-free survival (**left**) and disease-specific survival (**right**) of South Asian patients based on betel nut use.

4. Discussion

This study demonstrated that patients of SA ethnicity had significantly worse survival outcomes and were twice as likely to recur compared to non-SA patients even after accounting for other known factors contributing to poor oncological outcomes. The SA community is one of the largest and fastest growing minority groups in Canada based on the 2021 census [28]. Considering the migration patterns within the South Asian community and their correlation with the prevalence of OSCC, it is important to acknowledge the potential impact on health trends in Canada. Understanding these patterns can help promote public health initiatives and ensure that the unique needs of the South Asian population are met, fostering a more inclusive and supportive environment. Studies conducted in Malaysia [29,30], the UK [31], Australia [32], and South Africa [33] indicate that individuals of SA heritage are at higher risk of oral cancer than the non-SA population in those countries. A study in British Columbia, which has one of the highest South Asian immigrant populations in Canada, demonstrated a relative risk of developing OSCC of 1.33 and 1.66 for South Asian men and women, respectively, as compared with the non-SA population [34]. Anecdotally, the senior authors at our centre, who treat high volumes of OSCC, felt that year after year, SA patients represented a disproportionately larger ethnicity group than other ethnicities, and were recurring more frequently. The decision to formally evaluate outcomes based on SA ethnicity was therefore born out of concern for a potentially at-risk population in the hope to validate the need for a more tailored approach to treating this group of patients, as well as to build awareness and inform public health policy.

This study uniquely evaluates differences in oncological outcomes of patients of SA ethnicity affected by OSCCs compared to patients of non-SA ethnicity. These results suggest that, in Canada, SA ethnicity is an independent predictor of recurrence-free and worse

disease-specific survival when compared to non-SA patients. This study was conducted within the framework of a regional cancer center, where a dedicated multidisciplinary team, possessing expert training and extensive experience, oversees the management of all head and neck cancers. This setup intentionally minimizes bias for the selection for more complicated cases, given that all early- and advanced-stage cancers within the catchment area are treated at this centre. The stage of diagnosis is regarded as one of the most important predictors of oral cancer survival with a significantly improved 5-year survival rate for early-stage disease (71.4%) than for late-stage disease (21.8%) [35]. In this study, when comparing baseline characteristics of SA and non-SA patients, oncological parameters such as T-Stage, N-stage, ENE, LVI and PNI were similar, which suggests they were not the primary drivers of differences in recurrence and worse survival in SA patients. This association was also found in multivariable analysis. The similarity in these variables between groups also suggests that there are no discrepancies in access to care, which would likely lead to a delayed presentation, with more advanced disease at time of presentation. Although the initial presenting burden of disease is an imperfect tool to estimate access to care, in a universal health care system, access to care based on the financial resources of patients is relatively uniform across all sub-populations. Interestingly, features that are typically protective against developing OSCC, such as younger age and non-smoking status, were more common in SA patients. Despite this, being SA resulted in a two-fold increase in recurrence and decrease in OSCC survival. In addition, there was a statistically significant difference in age between the cohorts. While the difference was statistically significant, the clinical difference in mean age was only 4 years. To ensure that age would not confound the results, this variable was added to the multivariate model and was found not to have an impact on the result. As expected, patients with advanced T stage (T3/4), nodal disease and ENE had both worsened DSS and RFS, proving that the patient cohort in this study is representative of the greater head and neck cancer population. Disease stage at time of diagnosis has been previously identified as a causative factor in poorer oncological outcome in minority groups [36]. In this study, even after controlling for disease stage, SA ethnicity remained as an independent factor in predicting survival and recurrence.

Several factors potentially contribute to the poorer outcomes of OSCC in SA patients. One of the major factors is thought to be the use of betel nut in the SA culture, which is commonly consumed in the form of betel quid. Although the added tobacco plays a significant role in the development of OSCCs, studies have suggested that betel products, which contain arecoline and 3-(methylnitrosamino) propionitrile, may have an independent carcinogenic effect [37], resulting in malignant transformation of oral submucosal fibrosis (OSMF). The potential for malignant transformation resulting in OSCC has been reported to be as high as 7 to 13% [38]. Although the exact mechanism is not well understood, betel nut is thought to induce c-jun proto-oncogene expression in human mucosal fibroblasts [39]. Fibrosis itself can result in decreased vascularity and hypoxia, thus mediating mutated cell divisions [40]. This study did not find any differences on either recurrence or survival among patients of SA ethnicity based on betel nut use; however, given that betel nut consumption was not consistently reported in patient charts, further investigation with larger numbers and more consistent reporting is required to verify this finding.

The pattern of recurrence describes whether a patient recurs locally, regionally, or at a distant site. Given that betel nut is often stored inside the cheek for prolonged periods of time, one would expect SA patients to recur locoregionally if betel nut use is the causative factor. In our study population, the majority of recurrences in the SA population were local/regional; however, the proportion of patients that recurred locoregionally was not significantly different between SA and non-SA patients. This suggests that regardless of the causative agent for OSCC, recurrences are more likely to manifest as local/regional rather than distant disease.

A strength of this study is that it relies on the rigorous, prospective collection of data including patient-related factors, tumor factors, treatment factors and oncologic outcomes. The limitations that are associated with the retrospective design are somewhat mitigated

by the fact that the data points were recorded prospectively. A limitation is the relatively small sample size within the SA cohort. Despite this, the fact that SA ethnicity was an independent and statistically significant predictor of worsened outcome would suggest that sample size did not detract from the clinical findings of the study. A larger multicenter study could yield more definitive results on this issue. Given the absence of race or ethnicity information in many databases and registries used in health research, surnames are frequently employed as a proxy when investigating healthcare patterns within ethnic populations. Despite this, a limitation arises in potentially excluding individuals of South Asian background who may have undergone name changes. However, it should be noted that in Canada, according to the 2021 census, 76% of South Asians were recent immigrants born outside of Canada [28], and therefore, the likelihood of experiencing a name change is low. This study also did not differentiate between SA immigrants and Canadian-born people of SA ethnicity (first and subsequent generations), which hinders the ability to distinguish between the role of environment versus inheritance on the findings. There are important factors related to immigration status that may mediate the findings of this study, some of which include betel nut use, environmental factors and genetic factors. Although, there are no specific data on the use of betel nut in Canada, UK and Australian data show that it is commonly used among first-generation immigrants and its use is reduced in subsequent generations [41]. However, in younger generations, the form of consumption is tilting towards ingestion, which may result in higher rates of esophageal cancers [39]. As such, a more granular study on time since immigration and mode of betel nut use would be informative. In addition to environmental factors, genetics can also play a role in the poor outcomes observed in South Asian patients with OSCC. However, no specific genes have been identified as predisposing factors for OSCC in the SA population, and the hereditary factors that contribute to the disease are largely unknown. While most cases of OSCC occur sporadically, certain families with a high preponderance of the disease have been found to carry oncogenes such as VAV2 and IQGAP1 with an autosomal dominance penetrance [42]. Moreover, with the emergence of precision medicine, there has been a growing interest in identifying diagnostic and prognostic biomarkers for OSCC. One such biomarker is microRNA (miRNA), a large group of small single-stranded non-coding endogenous RNAs that play a role in post-transcriptional gene regulation. The upregulation of miRNAs is thought to contribute to OSCC resistance to chemoradiation and recurrence [43]. Our centre is involved in banking the tumors of all consecutive OSCC patients and intends to explore the potential molecular basis of poor OSCC outcomes in the SA population.

The findings of this study reveal that patients with SA ethnicity experience significantly poorer outcomes compared to the non-SA cohort, even after accounting for other predictors of poor outcome. To gain a more comprehensive understanding of the intricate interplay between ethnicity, environmental exposure, and genetic predisposition in OSCC outcomes, further research is imperative. Such research could pave the way for personalized treatment decisions and patient counseling, as well as the formulation of public health policies that serve to assist vulnerable and at-risk populations.

5. Conclusions

Patients of SA ethnicity had worse outcomes (higher risk of recurrence and worsened survival) than patients with non-SA ethnicity, even after controlling for other known predictors of poor outcome in OSCC. These findings can inform more individualized treatment decision making and impact public health policy when serving heterogeneous patient populations.

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Informed Consent Statement: Patient consent was waived due to the fact that any data abstracted did not involve contact with patients. Rather, the data were abstracted from our prospective, deidentified database. Not patients were identified in this study.

Data Availability Statement: Data for this study are housed locally on a database (Otobase©). This database is maintained daily. Data are linked to patient identifiers, and therefore not available for public viewing. The de-identified data and analysis are available to researchers upon request.

Conflicts of Interest: The authors declare no conflicts of interest.

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